

FORM PTO 1390  
(REV 5-93)

US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NUMBER  
2001\_1930A

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. §371

U.S. APPLICATION NO.  
(If known, enter 37 CFR 2.5)  
New **10/019693**

International Application No.  
PCT/JP00/04427

International Filing Date  
July 4, 2000

Priority Date Claimed  
July 6, 1999

Title of Invention  
PHENYL SULFAMATE DERIVATIVES


Applicant(s) For DO/EO/US  
Naoyuki KOIZUMI, Makoto OKADA, Shigeki IWASHITA, Shigehiro TAKEGAWA,  
Takayoshi NAKAGAWA, Hiroo TAKAHASHI and Tomohito FUJI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. §371(c)(2)). **ATTACHMENT A**
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3)).
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19.
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)). **ATTACHMENT B**
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. **ATTACHMENT C**
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. **ATTACHMENT D**
13. ☒ A **FIRST** preliminary amendment. **ATTACHMENT E**  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☒ Other items or information:
  - ☒ a. Cover Page of Published International Application No. WO 01/02349 **ATTACHMENT F**
  - ☒ b. International Search Report **ATTACHMENT G**

U.S. APPLICATION NO. <b>10/019693</b> New		INTERNATIONAL APPLICATION NO. PCT/JP00/04427		ATTORNEY'S DOCKET NO. 2001 1930A					
15. [X] The following fees are submitted  <b>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):</b> Neither international preliminary examination fee nor international search fee paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1040.00 International Search Report has been prepared by the EPO or JPO ..... \$ 890.00 International preliminary examination fee not paid to USPTO but international search paid to USPTO ..... \$ 740.00 International preliminary examination fee paid to USPTO but claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$ 690.00 International preliminary examination fee paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$ 100.00  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <th style="width:50%;">CALCULATIONS</th> <th style="width:50%;">PTO USE ONLY</th> </tr> <tr> <td style="height: 100px; vertical-align: bottom;">\$890.00</td> <td></td> </tr> </table>		CALCULATIONS	PTO USE ONLY	\$890.00	
CALCULATIONS	PTO USE ONLY								
\$890.00									
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$					
Claims	Number Filed	Number Extra	Rate						
Total Claims	17 -20 =	0	X \$18.00	\$					
Independent Claims	2 -3 =	0	X \$84.00	\$					
Multiple dependent claim(s) (if applicable)			+ \$280.00	\$					
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$890.00					
<input type="checkbox"/> Small Entity Status is hereby asserted. Above fees are reduced by 1/2.				\$					
<b>SUBTOTAL =</b>				\$890.00					
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	\$				
<b>TOTAL NATIONAL FEE =</b>				\$890.00					
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40 per property				+	\$40.00				
<b>TOTAL FEES ENCLOSED =</b>				\$930.00					
				Amount to be refunded	\$				
				Amount to be charged	\$				
a. [X] A check in the amount of \$930.00 to cover the above fees is enclosed. A duplicate copy of this form is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. 23-0975 in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975.									
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b))          must be filed and granted to restore the application to pending status.</b>									
19. CORRESPONDENCE ADDRESS  <div style="text-align: center;">   <b>000513</b>          PATENT TRADEMARK OFFICE       </div>			By: <u>Matthew Jacob</u> Matthew Jacob, Registration No. 25,154  WENDEROTH, LIND & PONACK, L.L.P. 2033 "K" Street, N.W., Suite 800 Washington, D.C. 20006-1021 Phone: (202) 721-8200 Fax: (202) 721-8250  January 3, 2002						

THE COMMISSIONER IS AUTHORIZED  
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ACCOUNT NO. 23-0975

[CHECK NO.]

48209

[2001\_1930A]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Naoyuki KOIZUMI et al. :

Attn: BOX PCT

Serial No. New :

Docket No. 2001\_1930A

Filed January 3, 2002 :

PHENYL SULFAMATE DERIVATIVES  
[Corresponding to PCT/JP00/04427  
Filed July 4, 2000]

THE COMMISSIONER IS AUTHORIZED  
TO CHARGE ANY DEFICIENCY IN THE  
FEES FOR THIS PAPER TO DEPOSIT  
ACCOUNT NO. 23-0975

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents,  
Washington, DC 20231

Sir:

Please amend the above-identified application as follows, in order to eliminate multiple claim dependencies.

In the Claims:

Please amend claims 3-5 and 12-17 as follows.

3. (Amended) A phenyl sulfamate derivative or a salt thereof as claimed in claim 1 wherein R<sup>3</sup> represents a hydrogen atom or a halogen atom.

4. (Amended) A phenyl sulfamate derivative or a salt thereof as claimed in claim 1 wherein A is located at the 4-position.

5. (Amended) A phenyl sulfamate derivative or a salt thereof as claimed in claim 1 wherein A represents a substituted phenyl group or a group of the formula -X-NR<sup>4</sup>R<sup>5</sup>.

12. (Amended) A steroid sulfatase inhibitor containing, as an active ingredient, a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in claim 1.

13. (Amended) An agent for the treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease, which contains, as an active ingredient, a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in claim 1.

14. (Amended) A pharmaceutical composition comprising a phenyl sulfamate derivative formula (I) or a salt thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant.

15. (Amended) The use of a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in claim 1, for the prophylaxis or treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease.

16. (Amended) A method for the prophylaxis or treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease in a human being or other mammal which comprises administering a phenyl sulfamate derivative formula (I) or a salt thereof as claimed in claim 1, to a human being or other mammal.

17. (Amended) The use of a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in claim 1, for the preparation of an agent for treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease.




**REMARKS**

The above claim amendments are presented in order to remove multiple claim dependencies, so as to reduce the required filing fee.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attachment page is captioned "**Version With Markings to Show Changes Made.**"

Respectfully submitted,

Naoyuki KOIZUMI et al.

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January 3, 2002

group, and  $R^5$  represents a group other than a substituted or unsubstituted phenylcarbonyl group;

② when  $R^4$  represents a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, or a sulfamoyl group, X represents  $CH_2$  and  $R^5$  represents a group other than a substituted or unsubstituted phenylcarbonyl group; and

③ when  $R^5$  represents a substituted or unsubstituted phenylcarbonyl group, X represents  $CH_2$  and  $R^4$  represents a group other than a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl group]; or

$R^3$  and A, together with the phenyl group to which they are attached, represent a fluoren-2-yl or 9-oxofluoren-2-yl group;

provided that, when  $R^3$  represents a hydrogen atom, A does not represent an unsubstituted phenyl group.

2. A phenyl sulfamate derivative or a salt thereof as claimed in claim 1 wherein both  $R^1$  and  $R^2$  represent hydrogen atoms.

3. A phenyl sulfamate derivative or a salt thereof as claimed in claim 1 or 2 wherein  $R^3$  represents a hydrogen atom or a halogen atom.

4. <sup>Claim 1</sup> A phenyl sulfamate derivative or a salt thereof as claimed in ~~any of claims 1 to 3~~ wherein A is located at the 4-position.

5. <sup>Claim 1</sup> A phenyl sulfamate derivative or a salt thereof as claimed in ~~any of claims 1 to 4~~ wherein A represents a substituted phenyl group or a group of the formula  $-X-NR^4R^5$ .

6. A phenyl sulfamate derivative or a salt thereof as claimed in

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claim 5 wherein the substituted phenyl group is a phenyl group substituted by one or two substituents selected from halogen, lower alkyl, halogen-substituted lower alkyl, cyano-substituted lower alkyl, lower alkoxy, lower alkanoyloxy,  $-\text{OSO}_2\text{NR}^1\text{R}^2$ , organic sulfonyloxy, amino, lower alkanoylamino,  $-\text{NHSO}_2\text{NR}^1\text{R}^2$ , organic sulfonylamino, nitro, cyano, carboxyl and lower alkoxycarbonyl.

7. A phenyl sulfamate derivative or a salt thereof as claimed in claim 6 wherein, in the substituted phenyl group, the substituent or substituents are located at the 2- and/or 4-positions of the phenyl group.

8. A phenyl sulfamate derivative or a salt thereof as claimed in claim 5 wherein A represents a group of the formula  $-\text{X}-\text{NR}^4\text{R}^5$  and  $\text{R}^4$  represents a hydrogen atom, a lower alkyl group or a heteroaryl group.

9. A phenyl sulfamate derivative or a salt thereof as claimed in claim 8 wherein the heteroaryl group is a five- or six-membered monocyclic heteroaryl group containing 1 to 3 nitrogen atoms.

10. A phenyl sulfamate derivative or a salt thereof as claimed in claim 5 wherein  $\text{R}^5$  represents a substituted phenyl group.

11. A phenyl sulfamate derivative or a salt thereof as claimed in claim 10 wherein the substituted phenyl group is a phenyl group substituted by one or two substituents selected from hydroxyl, lower alkanoyloxy,  $-\text{OSO}_2\text{NR}^1\text{R}^2$ , nitro and cyano.

12. A steroid sulfatase inhibitor containing, as an active ingredient, a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in ~~any of claims 1 to 11.~~ <sup>claim 1</sup>

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13. An agent for the treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease, which contains, as an active ingredient, a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in <sup>Claim 1</sup> ~~any of claims 1 to 11~~.

14. A pharmaceutical composition comprising a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in <sup>Claim 1</sup> ~~any of claims 1 to 11~~, and a pharmaceutically acceptable adjuvant.

15. The use of a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in <sup>Claim 1</sup> ~~any of claims 1 to 11~~, for the prophylaxis or treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease.

16. A method for the prophylaxis or treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease in a human being or other mammal which comprises administering a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in <sup>Claim 1</sup> ~~any of claims 1 to 11~~, to the human being or other mammal.

17. The use of a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in <sup>Claim 1</sup> ~~any of claims 1 to 11~~, for the preparation of an agent for the treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease.

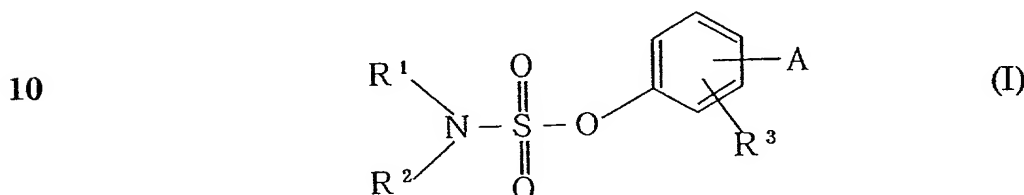
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## DESCRIPTION

## PHENYL SULFAMATE DERIVATIVES

Technical Field

- 5 This invention relates to novel phenyl sulfamate derivatives or salts thereof. More particularly, it relates to phenyl sulfamate derivatives represented by the following formula, or salts thereof.



wherein

- R¹ and R² each independently represent a hydrogen atom or a lower  
15 alkyl group;  
R³ represents a hydrogen atom, a halogen atom, a lower alkyl group,  
-OSO₂NR¹R², a lower alkanoylamino group, a nitro group or a cyano  
group; and  
A represents a substituted or unsubstituted phenyl group, a naphthyl  
20 group, a pyridyl group, 2-substituted thiazol-4-yl group, 3-substituted  
isoxazol-5-yl group, 1-cyano-2-(substituted or unsubstituted phenyl)vinyl  
group, 2-cyano-2-(substituted or unsubstituted phenyl)vinyl group, or a  
group of the formula -X-NR⁴R⁵ [in which X represents CO or CH₂, R⁴  
represents a hydrogen atom, a lower alkyl group, a substituted or  
25 unsubstituted phenyl group, a lower alkanoyl group, a substituted or  
unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower  
alkylsulfonyl group, a sulfamoyl group, a lower alkanoylamino group, a  
di(lower alkyl)amino group, a heteroaryl group, a heteroaryl-substituted  
lower alkyl group, or a substituted or unsubstituted phenylmethyl group,  
30 and R⁵ represents a hydrogen atom, a substituted or unsubstituted  
phenyl group, or a substituted or unsubstituted phenylcarbonyl group,

provided that

- ① when X represents CO, R<sup>4</sup> represents a group other than a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl group, and R<sup>5</sup> represents a group other than a substituted or unsubstituted phenylcarbonyl group;
- ② when R<sup>4</sup> represents a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, or a sulfamoyl group, X represents CH<sub>2</sub> and R<sup>5</sup> represents a group other than a substituted or unsubstituted phenylcarbonyl group; and
- ③ when R<sup>5</sup> represents a substituted or unsubstituted phenylcarbonyl group, X represents CH<sub>2</sub> and R<sup>4</sup> represents a group other than a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl group]; or
- R<sup>3</sup> and A, together with the phenyl group to which they are attached, represent a fluoren-2-yl or 9-oxofluoren-2-yl group; provided that, when R<sup>3</sup> represents a hydrogen atom, A does not represent an unsubstituted phenyl group.

### **Background Art**

Steroid sulfates such as dehydroepiandrosterone sulfate, cholesterol sulfate and estrone sulfate are intermediate products in the steroid metabolism within the human body. For example, estrone sulfate is hydrolyzed by steroid sulfatase present in the living body to yield estrone in free form. It is also known that, in the living body, this estrone is further converted reversibly into estradiol by the action of 17β-hydroxysteroid dehydrogenase. These estrogens formed in the steroid metabolism, such as estrone and estradiol, are considered to be closely associated with diseases such as breast cancer, uterine cancer, ovarian cancer, endometriosis, adenomyosis uteri and mastopathy.

Accordingly, it is believed that, if the action of steroid sulfatase can be effectively inhibited, this would be effective for the treatment of diseases associated with steroids such as estrogens. From this point of view, several steroidal compounds having an inhibitory effect on steroid sulfatase, as typified by estrone 3-sulfamate (EMATE), have been proposed (see Published Japanese Translation of PCT International Publication No. 501515/95).

However, although EMATE has a powerful inhibitory effect on steroid sulfatase, it also has a powerful estrogenic action and is hence a compound which is unsuitable for use as a drug for the treatment of diseases associated with estrogens.

Moreover, as nonsteroidal compounds having an inhibitory effect on steroid sulfatase, certain coumarin derivatives [e.g., 4-methylcoumarin 7-sulfamate (COUMATE)] have been proposed [see J. Med. Chem., Vol. 37, 219(1994)]. Furthermore, certain phenyl sulfamate derivatives [e.g., 4-(2-myristoylaminoethyl)phenyl sulfamate (DU-14)] have also been proposed [see J. Med. Chem., Vol. 39, 1349(1996)]. In addition, steroid sulfatase inhibitors having a specific ring system and a sulfamoyloxy group are also known (see U.S. Patent No. 6,011,024 and the pamphlet of International Publication of PCT Application No. WO2000/18397).

These nonsteroidal compounds such as COUMATE and DU-14 do not show an estrogenic action as a side effect. However, their principal action (i.e., their inhibitory effect on steroid sulfatase) is weak and, therefore, these compounds are not satisfactory as yet.

Japanese Patent Laid-Open No. 47162/91 and U.S. Patent No. 5,192,785 disclose certain sulfamate compounds. Although it is described therein that those compounds are useful as drugs for the treatment of chronic arthritis, osteoporosis, glaucoma and the like, neither mention nor suggestion is made of their inhibitory effect on steroid sulfatase.

The present inventors have now found that novel phenyl sulfamate derivatives in which the phenyl group is substituted by a specific substituent (e.g., substituted or unsubstituted phenyl, N-substituted aminomethyl, or N-substituted carbamoyl), or salts thereof exhibit a powerful inhibitory effect on steroid sulfatase without showing an estrogenic action as a side effect.

Thus, the present invention provides phenyl sulfamate derivatives represented by the above formula (I), or salts thereof.

#### Disclosure of the Invention

10       The term "lower" as used herein means that the group or compound modified by this term has 6 or less carbon atoms and preferably 4 or less carbon atoms.

Thus, examples of the "lower alkyl group" include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl and n-  
15   hexyl, and examples of the "lower alkoxy group" include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and n-hexyloxy. Moreover, examples of the "lower alkylenedioxy group" include methylenedioxy, ethylenedioxy and trimethylenedioxy, and examples of the "lower alkanoyl group" include acetyl, propionyl, butyryl, isobutyryl  
20   and pentanoyl.

The "lower alkanoylamino group" is an amino group substituted by the above-defined "lower alkanoyl group", and examples thereof include acetylamino, propionylamino and butyrylamino. The "di(lower alkyl)amino group" is an amino group di-substituted by the above-  
25   defined "lower alkyl group", and examples thereof include dimethylamino, diethylamino and dipropylamino. The "lower alkylsulfonyl group" is a sulfonyl group substituted by the above-defined "lower alkyl group", and examples thereof include methanesulfonyl and ethanesulfonyl.

30       "-OSO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>" is a sulfamoyloxy group whose N atom may optionally be mono- or di-substituted by the above-defined "lower alkyl



group". Examples thereof include, besides unsubstituted sulfamoyloxy, N-methylsulfamoyloxy, N,N-dimethylsulfamoyloxy and N,N-diethylsulfamoyloxy.

"-NHSO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>" is a sulfamoylamino group whose N atom may optionally be mono- or di-substituted by the above-defined "lower alkyl group". Examples thereof include, besides unsubstituted sulfamoylamino, N-methylsulfamoylamino, N,N-dimethylsulfamoylamino and N,N-diethylsulfamoylamino.

The "organic sulfonyloxy group" is a hydroxyl group substituted by an "organic sulfonyl group" which is a residue obtained by eliminating a hydroxyl group (OH) from an organic sulfonic acid, and preferred examples thereof include methanesulfonyloxy, p-toluenesulfonyloxy and benzenesulfonyloxy. The "organic sulfonylamino group" is an amino group substituted by the above-defined "organic sulfonyl group", and preferred examples thereof include methanesulfonylamino, p-toluenesulfonylamino and benzenesulfonylamino.

The "aralkyl group" is an alkyl group substituted by a monocyclic or polycyclic aryl group such as phenyl or naphthyl, and preferably an aryl-substituted lower alkyl group. Examples thereof include benzyl, 1-phenylethyl, 2-phenylethyl and 1-phenylpropyl.

In the "substituted or unsubstituted phenyl group" used in the definition of A, R<sup>4</sup> and R<sup>5</sup>, examples of the substituent(s) on the phenyl group include halogen, lower alkyl, halogen-substituted lower alkyl, cyano-substituted lower alkyl, hydroxyl, lower alkoxy, lower alkylendioxy, lower alkanoyloxy, sulfamoyloxy, N-(lower alkyl)sulfamoyloxy, N,N-di(lower alkyl)sulfamoyloxy, organic sulfonyloxy, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, sulfamoyloxy, N-(lower alkyl)sulfamoyloxy, N,N-di(lower alkyl)sulfamoyloxy, organic sulfonylamino, aralkyloxycarbonylamino, lower alkoxycarbonylamino, mercapto, lower alkylthio, lower alkanoylthio, nitro, cyano, carboxyl and lower alkoxycarbonyl, and the phenyl group

may be substituted by one to three substituents selected from the foregoing groups. Especially preferred examples of the substituted phenyl group are phenyl groups substituted by one or two substituents selected from halogen, lower alkyl, halogen-substituted lower alkyl, 5 cyano-substituted lower alkyl, lower alkoxy, lower alkanoyloxy, -OSO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, organic sulfonyloxy, amino, lower alkanoylamino, -NHSO<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>, organic sulfonylamino, nitro, cyano, carboxyl and lower alkoxycarbonyl.

Moreover, in the "substituted or unsubstituted phenylcarbonyl 10 group" used in the definition of R<sup>4</sup> and R<sup>5</sup>, examples of the substituent(s) on the phenyl group include the same groups as described above for the "substituted or unsubstituted phenyl group", and the phenyl group may be substituted by one to three substituents selected from them. Especially preferred examples of the substituted phenylcarbonyl group are 15 phenylcarbonyl groups whose phenyl group is substituted by one or two substituents selected from halogen, lower alkyl, lower alkoxy, sulfamoyloxy, nitro and cyano.

Furthermore, in the "substituted or unsubstituted phenylmethyl group" used in the definition of R<sup>4</sup>, examples of the 20 substituent(s) on the phenyl group include the same groups as described above for the "substituted or unsubstituted phenyl group", and the phenyl group may be substituted by one to three substituents selected from them. Especially preferred examples of the substituted phenylmethyl group are phenylmethyl groups whose phenyl group is 25 substituted by one or two substituents selected from halogen, lower alkyl, lower alkoxy, sulfamoyloxy, nitro and cyano.

In the "2-substituted thiazol-4-yl or 3-substituted isoxazol-5-yl" used in the definition of A, examples of the substituent include lower alkyl, nitro and cyano.

30 In the "heteroarylcarbonyl group", "heteroaryl group" and "heteroaryl-substituted lower alkyl group" used in the definition of R<sup>4</sup>,

the term "heteroaryl" means a monocyclic or polycyclic unsaturated heterocyclic group which contains 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur atoms and which includes a five- to seven-membered ring. Alternatively, the heterocyclic ring may further be fused with an aromatic hydrocarbon ring to form a fused ring. Among such heteroaryl groups, preferred ones are five- or six-membered monocyclic heterocyclic groups containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur atoms.

Thus, examples of such "heteroaryl groups" include pyrrolyl, furyl, thienyl, imidazolyl, pirazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyranyl, pyrimidinyl, pyridazinyl, pyrazinyl, azepinyl, purinyl, naphthyridinyl, pteridinyl, benzothienyl, benzofuranyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, chromenyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, phenanthridinyl, acridinyl and dibenzazepinyl.

When A represents a group of the formula  $-X-NR^4R^5$ , and X,  $R^4$  and/or  $R^5$  have a  $-CO-$  or  $-SO_2-$  moiety attached directly to the N atom in this formula, this group should not contain more than one such moiety. Accordingly, in the group of the formula  $-X-NR^4R^5$ , ① when X represents CO,  $R^4$  represents a group other than a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl group, and  $R^5$  represents a group other than a substituted or unsubstituted phenylcarbonyl group; ② when  $R^4$  represents a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, or a sulfamoyl group, X represents  $CH_2$  and  $R^5$  represents a group other than a substituted or unsubstituted phenylcarbonyl group; and ③ when  $R^5$  represents a substituted or unsubstituted phenylcarbonyl group, X represents  $CH_2$  and  $R^4$  represents a group other than a lower alkanoyl group, a substituted or

unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl group.

Moreover, the term "halogen atom" comprehends fluorine, chlorine, bromine and iodine atoms.

5           One preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which both  $R^1$  and  $R^2$  represent hydrogen atoms.

          Another preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which  $R^3$   
10       represents a hydrogen atom or a halogen atom.

          Still another preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which A is located at the 4-position.

          A further preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which A  
15       represents a substituted phenyl group or a group of the formula  $-X-NR^4R^5$ .

          Still a further preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which the  
20       substituted phenyl group defined for A is a phenyl group substituted by one or two substituents selected from halogen, lower alkyl, halogen-substituted lower alkyl, cyano-substituted lower alkyl, lower alkoxy, lower alkanoyloxy,  $-OSO_2NR^1R^2$ , organic sulfonyloxy, amino, lower alkanoylamino,  $-OSO_2NR^1R^2$ , organic sulfonylamino, nitro, cyano, car-  
25       boxyl and lower alkoxy carbonyl.

          Still a further preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which, in the substituted phenyl group defined for A, the substituent or substituents are located at the 2- and/or 4-positions of the phenyl group.

30           Still a further preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which A

represents a group of the formula  $-X-NR^4R^5$  and  $R^4$  represents a hydrogen atom, a lower alkyl group or a heteroaryl group.

Still a further preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which the

5 heteroaryl group defined for  $R^4$  is a five- or six-membered monocyclic heteroaryl group containing 1 to 3 nitrogen atoms.

Still a further preferred class of compounds in accordance with the present invention are the compounds of formula (I) in which  $R^5$  represents a substituted phenyl group, such as a phenyl group substituted by one or two substituents selected from hydroxyl, lower

10 alkanoyloxy,  $-OSO_2NR^1R^2$ , nitro and cyano.

In addition to the compounds described in the examples which will be given later, typical examples of the compounds of the above formula (I) which are provided by the present invention include:

- 15 2'-nitrobiphenyl-4-yl N-methylsulfamate,  
 2'-cyanobiphenyl-4-yl N,N-dimethylsulfamate,  
 4'-nitrobiphenyl-4-yl N,N-dimethylsulfamate,  
 4-[N-(4-cyanophenyl)-N-(1,2,4-triazol-4-yl)aminomethyl]phenyl N,N'-dimethylsulfamate,
- 20 2'-bromobiphenyl-4-yl sulfamate,  
 4'-methylbiphenyl-4-yl sulfamate,  
 4'-hydroxybiphenyl-4-yl sulfamate,  
 3',4'-methylenedioxybiphenyl-4-yl sulfamate,  
 4'-sulfamoyloxybiphenyl-4-yl acetate,
- 25 biphenyl-4,4'-diyl 4-(N,N-dimethylsulfamate) 4'-sulfamate,  
 4'-aminobiphenyl-4-yl sulfamate,  
 4'-acetylaminobiphenyl-4-yl sulfamate,  
 4'-dimethylaminobiphenyl-4-yl sulfamate,  
 4'-sulfamoyloxybiphenyl-4-carboxylic acid,
- 30 4'-methylthiobiphenyl-4-yl sulfamate,  
 2'-cyanobiphenyl-4,4'-diyl disulfamate,

- 2'-cyano-4'-trifluoromethylbiphenyl-4-yl sulfamate,  
methyl 2'-cyano-4'-sulfamoyloxy-4-biphenylcarboxylate,  
2'-cyano-4'-cyanomethylbiphenyl-4-yl sulfamate,  
4-cyanobiphenyl-2,4'-diyl disulfamate,
- 5 biphenyl-2,4,4'-triyl trisulfamate,  
3-chloro-2'-cyanobiphenyl-4-yl sulfamate,  
3-chloro-4'-nitrobiphenyl-4-yl sulfamate,  
3-chlorobiphenyl-4,4'-diyl disulfamate,  
3-chloro-2'-cyano-4'-nitrobiphenyl-4-yl sulfamate,
- 10 2-methyl-2'-nitrobiphenyl-4-yl sulfamate,  
2'-cyano-2,4'-dinitrobiphenyl-4-yl sulfamate,  
2-nitrobiphenyl-4,4'-diyl disulfamate,  
2,4'-dicyanobiphenyl-4-yl sulfamate,  
4-(2-pyridyl)phenyl sulfamate,
- 15 4-(2-cyanothiazol-4-yl)phenyl sulfamate,  
4-(3-methylisoxazol-5-yl)phenyl sulfamate,  
4-[N-(4-sulfamoyloxyphenyl)aminomethyl]phenyl sulfamate,  
methyl 4-[N-(4-sulfamoyloxybenzoyl)amino]benzoate,  
4-[N-(4-bromophenyl)carbamoyl]phenyl sulfamate,
- 20 4-[N-(4-trifluoromethylphenyl)carbamoyl]phenyl sulfamate,  
4-[N-(4-nitrophenyl)carbamoyl]phenyl sulfamate,  
4-[N-(4-cyanomethylphenyl)carbamoyl]phenyl sulfamate,  
4-[N-(2-cyano-4-nitrophenyl)carbamoyl]phenyl sulfamate,  
4-[N-ethyl-N-(4-sulfamoyloxyphenyl)aminomethyl]phenyl sulfamate,
- 25 4-[N-(4-cyanophenyl)-N-(4-sulfamoyloxyphenyl)carbamoyl]phenyl  
sulfamate,  
4-[N,N-di(4-sulfamoyloxyphenyl)carbamoyl]phenyl sulfamate,  
4-[N-(4-acetyl-N-(4-cyanophenyl)aminomethyl]phenyl sulfamate,  
4-[N-benzoyl-N-(4-sulfamoyloxybenzyl)amino]phenyl sulfamate,
- 30 4-(sulfamoylaminomethyl)phenyl sulfamate,  
4-[N'-acetyl-N-(4-sulfamoyloxyphenyl)hydrazinocarbonyl]phenyl

sulfamate,

4-(N',N'-dimethyl-N-phenylhydrazinocarbonyl)phenyl sulfamate,

4-[N-(4-sulfamoyloxyphenyl)-N-(1,2,4-triazol-4-yl)carbamoyl]-  
phenyl sulfamate,

5 4-[N-(2-nitrophenyl)-N-(1,2,4-triazol-4-yl)carbamoyl]phenyl sulfamate,

4-[N-(4-nitrophenyl)-N-(1,2,4-triazol-4-yl)aminomethyl]phenyl sulfamate,

4-[N-(2-cyanophenyl)-N-(1,2,4-triazol-4-yl)aminomethyl]phenyl  
sulfamate,

4-[N-(4-cyanophenyl)-N-(pyrazol-1-yl)aminomethyl]phenyl sulfamate,

10 4-[N-(4-cyanophenyl)-N-(imidazol-1-yl)aminomethyl]phenyl sulfamate,

4-[N-(4-cyanophenyl)-N-(tetrazol-1-yl)aminomethyl]phenyl sulfamate,

4-[N-benzoyl-N-ethylaminomethyl]phenyl sulfamate,

2-chloro-4-[N-(4-cyanophenyl)-N-(1,2,4-triazol-4-yl)amino-  
methyl]phenyl sulfamate,

15 4-[N-(4-cyanophenyl)-N-(1,2,4-triazol-4-yl)aminomethyl]-3-  
nitrophenyl sulfamate,

2'-cyanobiphenyl-3-yl sulfamate

biphenyl-3,4'-diyl disulfamate, and

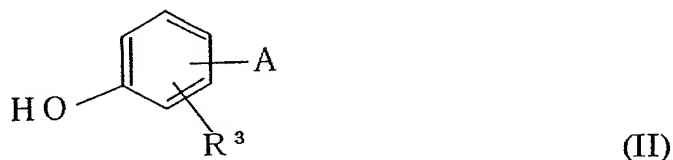
2'-cyano-4'-nitrobiphenyl-3-yl sulfamate.

20            Depending on the type of substituent A, the compounds of  
formula (I) in accordance with the present invention may optionally form  
salts. Examples of such salts include salts formed with inorganic acids  
such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and  
phosphoric acid; salts formed with organic acids such as acetic acid,  
25 oxalic acid, citric acid, lactic acid, tartaric acid and p-toluenesulfonic  
acid; alkali metal salts such as sodium, potassium and lithium salts;  
alkaline earth metal salts such as calcium and magnesium salts; salts  
formed with organic bases such as triethylamine, dicyclohexylamine,  
pyrrolidine, morpholine and pyridine; and ammonium salts. Among  
30 others, pharmaceutically acceptable salts are preferred.

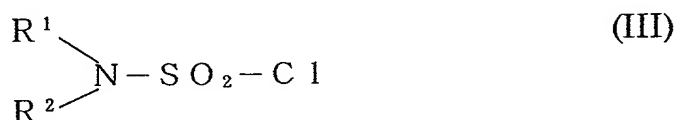
According to the present invention, the compounds of the

above formula (I) may be prepared, for example, by reacting an phenol derivative of the formula

5



wherein A and R<sup>3</sup> have the above-defined meanings, with an  
10 amidosulfonic acid chloride of the formula



15 wherein R<sup>1</sup> and R<sup>2</sup> have the above-defined meanings.

This reaction may generally be carried out in an inert solvent selected, for example, from amides such as N,N-dimethylformamide and N-methylpyrrolidone; alkyl halides such as dichloromethane and dichloroethane; and organic bases such as pyridine, optionally in the  
20 presence of an alkali such as sodium hydride, sodium methoxide, potassium butoxide, potassium hydroxide or potassium phosphate, or an organic base such as triethylamine or 2,6-di-tert-butyl-4-methylpyridine, at a temperature ranging from about -20°C to the reflex temperature of the reaction mixture and preferably from about 0°C to room  
25 temperature.

No particular limitation is placed on the proportion of the amidosulfonic acid chloride of formula (III) to the compound of formula (II). However, the amidosulfonic acid chloride may generally be used in an amount of at least 1 mole, preferably about 1.1 to 20 moles, and more  
30 preferably about 2 to 10 moles, per mole of the compound of formula (II). Moreover, the aforesaid alkali is suitably used in an amount of



about 2 to about 10 moles per mole of the compound of formula (II).

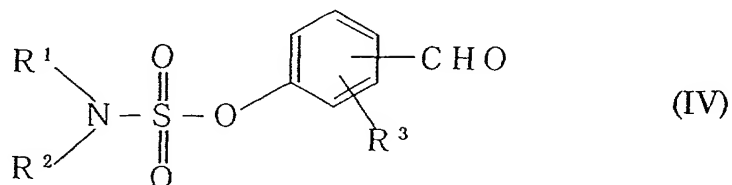
The compounds of the above formula (I) in which both  $R^1$  and  $R^2$  represent hydrogen atoms may also be prepared by reacting a phenol derivative of the above formula (II) with chlorosulfonyl isocyanate and then treating the resulting product with water.

The aforesaid reaction of the phenol derivative of formula (II) with chlorosulfonyl isocyanate may generally be carried out in an inert solvent selected, for example, from aromatic hydrocarbons such as toluene and xylene; halogenated aromatic hydrocarbons such as chlorobenzene and dichlorobenzene; and acetonitrile, at a temperature ranging from 50°C to the reflex temperature of the reaction mixture and preferably from 80°C to the reflex temperature of the reaction mixture.

No particular limitation is placed on the proportion of chlorosulfonyl isocyanate to the phenol derivative of formula (II). However, chlorosulfonyl isocyanate may generally be used in an amount of at least 1 mole and preferably about 1.01 to 2 moles, per mole of the compound of formula (II).

The subsequent treatment with water may usually be carried out simply by adding water to the reaction mixture resulting from the aforesaid reaction.

The compounds of the above formula (I) in which X represents  $CH_2$ ,  $R^5$  represents a hydrogen atom, and  $R^4$  represents a group other than a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl group may also be prepared, for example, by reacting an aldehyde compound of the formula



wherein  $R^1$ ,  $R^2$  and  $R^3$  have the above-defined meanings, with an amino compound of the formula



5

wherein  $R^{41}$  represents a hydrogen atom, a lower alkyl group, a substituted or unsubstituted phenyl group, a lower alkanoylamino group, a di(lower alkyl)amino group, a heteroaryl group, a heteroaryl-substituted lower alkyl group, or a substituted or unsubstituted phenylmethyl group; and reducing the Schiff base so formed.

10

The aforesaid reaction of the aldehyde compound of formula (IV) with the amino compound of formula (V) may generally be carried out in the absence of solvent, or in a solvent selected from water; alcohols such as methanol and ethanol; ethers such as diethyl ether, tetrahydrofuran, dimethoxyethane and dioxane; alkanolic acids such as acetic acid and propionic acid; and amides such as dimethylformamide and dimethylacetamide, at a temperature ranging from 0°C to the reflux temperature of the reaction mixture and preferably from room temperature to 100°C.

15

20

No particular limitation is placed on the proportion of the amino compound of formula (V) to the aldehyde compound of formula (IV). However, the amino compound of formula (V) may generally be used in an amount of at least 1 mole, preferably about 1.1 to 20 moles, and more preferably about 2 to 10 moles, per mole of the compound of formula (IV).

25

The reduction of the Schiff base may usually be carried out simply by adding a complex metal hydride (e.g., sodium borohydride or sodium cyanoborohydride) to the reaction mixture containing the Schiff base formed and reacting this mixture at a reaction temperature ranging from about 0°C to room temperature.

30

Thus, the compounds of the above formula (I) which are

desired in the present invention can be formed.

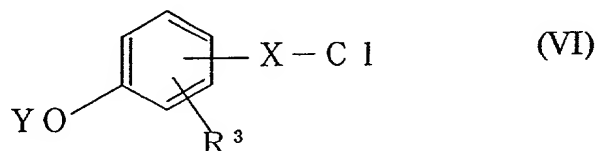
Among the compounds of the above formula (II) which are used as starting materials in the aforesaid reactions, most of the compounds in which A represents a substituted or unsubstituted phenyl group, a naphthyl group, a pyridyl group, a 4-substituted thiazol-2-yl group, a 3-substituted isoxazol-5-yl group, a 1-cyano-2-(substituted or unsubstituted phenyl)vinyl group, or a 2-cyano-2-(substituted or unsubstituted phenyl)vinyl group are known compounds described in the literature of the prior art. In the case of novel compounds, they may be easily prepared in the same manner as the known compounds. For example, the compounds of formula (II) in which A represents a substituted phenyl group may be prepared by reacting a substituted phenyl halide compound with a 4-methoxyphenylboric acid compound and eliminating the hydroxyl-protecting group of the resulting substituted anisole compound with the aid of a Lewis acid (e.g., boron tribromide or aluminum chloride) or an acid (e.g., hydrobromic acid). For details on the reaction conditions and the like, refer to Preparation Examples 1 and 2 which will be given later.

On the other hand, most of the compounds of the above formula (II) in which A represents  $-X-NR^4R^5$  are novel compound which have not been described in the literature of the prior art. Depending on the type of the substituent  $R^5$ , they may be prepared, for example, by following the pathway shown in Reaction Scheme 1 or 2 given below. For details on the reaction conditions and the like, refer to Preparation Examples 7-11, 14, 20, 22, 23, 25, 28, 29, 31, 34, 35, 38, 47 and 52 which will be given later.

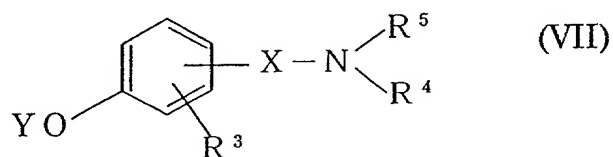
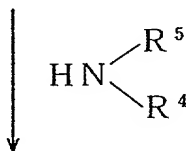
When  $R^5$  represents a hydrogen atom or a substituted or unsubstituted phenyl group:

Reaction Scheme 1

5



10



15



- ①  $R^4$  is converted to another group as required.
- ② The protecting group Y is eliminated.

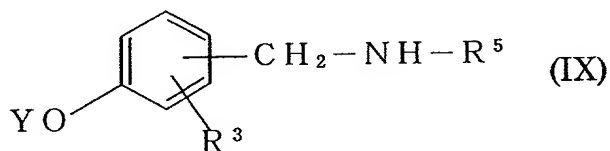
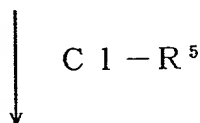
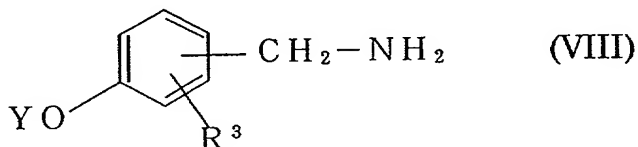
20

(II)

In the above formulas, Y represents a hydroxyl-protecting group; and X,  $R^3$ ,  $R^4$  and  $R^5$  have the above-defined meanings.

When  $R^5$  represents a substituted or unsubstituted phenylcarbonyl group:

Reaction Scheme 2

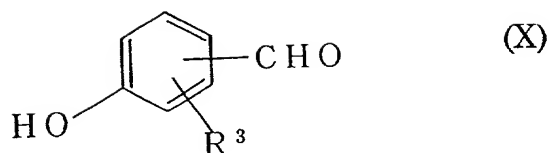


- ① Hydrogen atoms are converted to other  $R^4$  groups as required.
- ② The protecting group Y is eliminated.

20 In the above formulas, Y,  $R^3$ ,  $R^4$  and  $R^5$  have the above-defined meanings.

Moreover, most of the aldehyde compounds of the above formula (IV) which are used as starting materials in the aforesaid reaction are novel compounds which have not been described in the literature of the prior art. They may be easily prepared, for example, by reacting an aldehyde compound of the formula

25



- 5 wherein  $R^3$  has the above-defined meaning, with an amidosulfonic acid chloride of the above formula (III) in the same manner as described in connection with the reaction of a compound of the above formula (II) with an amidosulfonic acid chloride of the above formula (III). For details on the reaction conditions of this reaction, and the like, refer to
- 10 Preparation Example 24 which will be given later.

When the compounds used in each of the aforesaid reactions contain substituents (e.g., hydroxyl, amino and carboxyl) which may participate in the reaction, these substituents may be protected by protecting groups as required. These protected by protecting groups

15 may be eliminated after completion of the reaction.

Thus, the compounds of the above formula (I) which are formed according to the processes of the present invention may be isolated and purified from the reaction mixture by per se known techniques such as recrystallization, distillation, column chromatography and thin-layer

20 chromatography.

The above-described phenyl sulfamate derivatives of formula (I) or salts thereof in accordance with the present invention have a powerful inhibitory effect on steroid sulfatase and are hence effective for the treatment of diseases associated with steroids (e.g., estrogens), such

25 as breast cancer, corpus uteri cancer, ovarian cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, hysterosarcoma, autoimmune diseases, dementia, Alzheimer's disease, mastopathy, gynecomastia in the male, prostatomegaly, and male infertility due to oligospermia.

30 The inhibitory effect on steroid sulfatase of compounds of formula (I) in accordance with the present invention can be measured

according to the following procedure.

(1) Measurement of an in vitro inhibitory effect on steroid sulfatase

Six-well plates (9.4 cm<sup>2</sup>/well) were inoculated with intact MCF-7 human breast cancer cells at a density of about  $1 \times 10^5$  cells/well. Using  
 5 Dulbecco's modified Eagle medium (DMEM) containing 10 mM HEPES, 5% fetal bovine serum, 0.011% sodium pyruvate and 0.37% sodium bicarbonate, the cells were grown to 80% confluency.

The plates were washed with Earle's balanced salt solution (EBSS from Life Technologies Inc., Grand Island, N.Y., USA). Then,  
 10 serum-free DMEM (2 ml) containing 4 pmol ( $4.4 \times 10^5$  dpm) of [6,7-<sup>3</sup>H]estrone 3-sulfate (with a specific activity of 49 Ci/mmol; from New England Nuclear, Boston, Mass., USA), together with a test compound, was placed on each plate and incubated at 37°C for 20 hours. After incubation, the plate was cooled, and the medium (1 ml) was  
 15 pipetted into a separating tube containing [4-<sup>14</sup>C]estrone ( $6 \times 10^3$  dpm) (with a specific activity of 52.5 mCi/mmol; from New England Nuclear, Boston, Mass., USA). This mixture, together with toluene (4 ml), was vigorously shaken for 30 seconds. It was shown by experiment that more than 90% of [4-<sup>14</sup>C]estrone was removed from the aqueous layer by  
 20 this treatment. A portion (2 ml) of the organic phase was taken, and the <sup>3</sup>H and <sup>14</sup>C contents thereof were measured by scintillation spectrometry. Then, the amount of estrone 3-sulfate hydrolyzed was calculated from the total <sup>3</sup>H count (corrected for the volumes of the medium used and the organic phase, and for the recovery of the  
 25 [<sup>14</sup>C]estrone added) and the specific activity of the substrate. The results thus obtained are shown in the following Table 1.

Table 1

	<u>Example No. of compound</u>	<u>Inhibitory rate (<math>3 \times 10^{-9}</math> M, %)</u>
	Example 3	76
	Example 23	67
5	Example 25	87
	Example 27	94

(2) Measurement of an in vivo inhibitory effect on steroid sulfatase

A test compound was suspended in a 0.5% polyoxyethylene (20) sorbitan monooleate solution (Tween 80) and administered, once a day, to a group of 5 female SD strain rats (weighing 168-194 g) for 5 days.

Four hours after the final administration, all rats were sacrificed by ether anesthesia and dissected. Thus, the liver and the uterus were excised from each rat, washed once with cold phosphate-buffered saline (PBS, pH 7.4), and preserved at -70°C or below. Each of the liver and the uterus was finely minced with scissors, and suspended in PBS containing 250 mM sucrose (5 ml/g tissue). Under cooling with ice, each suspension was homogenized with an Ultra-Turrax homogenizer. The resulting homogenate was centrifuged (at 4°C) at 20 2,000xg for 30 minutes to remove nuclei and cell debris, and the protein concentration in this supernatant was measured according to the method of Bradford [Anal. Biochem. 72, 248-254(1976)].

The homogenate in an amount corresponding to a protein concentration of 100-500 µg/ml was mixed with [6,7-<sup>3</sup>H]estrone 3-sulfate (with a specific activity of 49 Ci/mmol; from New England Nuclear, Boston, Mass., USA) in an amount corresponding to a substrate concentration of 20 µM. This mixture was diluted with PBS to a total volume of 1 ml, and incubated at 37°C for 30 minutes. After incubation (1 ml), the steroid sulfatase activity was determined in the same manner as described above for the in vitro measurement (1). The results thus obtained are shown in the following Table 2.



Table 2

	<u>Example No. of compound</u>	<u>Inhibitory rate (0.5 mg/kg, p.o., %)</u>	
		<u>Liver</u>	<u>Uterus</u>
	Example 1	91.2	94.9
5	Example 3	95.4	93.8
	Example 16	97.0	100
	Example 21	97.2	97.6
	Example 25	99.5	100
	Example 38	85.3	79.0

10

Thus, the compounds of formula (I) or salts thereof in accordance with the present invention are useful as steroid sulfatase inhibitors and can hence be used for therapeutic purposes in human beings and other mammals by oral or parenteral administration (e.g., intramuscular injection, intravenous injection, intrarectal administration or percutaneous administration).

When the compounds of the present invention are used as drugs, they may be made into in any of various pharmaceutical preparations (or pharmaceutical compositions) according to the intended purpose. These pharmaceutical preparations include solid preparations (e.g., tablets, hard capsules, soft capsules, granules, powders, fine subtilaes, pills and troches), semisolid preparations (e.g., suppositories and ointments), and liquid preparations (e.g., injections, emulsions, suspensions, lotions and sprays). Pharmaceutically acceptable adjuvants which can be used in the aforesaid pharmaceutical preparations include, for example, starch, gelatin, glucose, lactose, fructose, maltose, magnesium carbonate, talc, magnesium stearate, methylcellulose, carboxymethylcellulose or salts thereof, acacia, polyethylene glycol, alkyl esters of p-hydroxybenzoic acid, syrup, ethanol, propylene glycol, petrolatum, carbowax, glycerin, sodium chloride, sodium sulfite, sodium phosphate and citric acid. The aforesaid pharmaceutical preparations

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may also contain other therapeutically useful drugs.

The content of the compounds of the present invention in the aforesaid pharmaceutical preparations may vary according to the dosage form. Generally, it is desirable that solid and semisolid preparations  
5 contain the compounds of the present invention at a concentration of 0.1 to 50% by weight and liquid preparations contain them at a concentration of 0.05 to 10% by weight.

The dosage of the compounds of the present invention may vary widely according to the type of the warm-blooded animal (including  
10 human being) to be treated, the route of administration, the severity of symptoms, the diagnosis made by the doctor, and the like. Generally, they may be administered in a daily dose of 0.01 to 5 mg/kg and preferably 0.02 to 2 mg/kg. However, it is a matter of course that they may be administered in doses less than the lower limit of the aforesaid range or  
15 greater than the upper limit thereof, depending on the severity of symptoms in the patient and the diagnosis made by the doctor. The aforesaid daily dose may be given at a time or in several divided doses.

#### Examples

The present invention is more specifically explained with  
20 reference to the following examples and preparation examples.

#### Example 1

108 mg of 2'-nitrobiphenyl-4-ol was dissolved in 1.5 ml of N,N-dimethylformamide, and a suspension of 120 mg of sodium hydride in 1.5 ml of N,N-dimethylformamide was added thereto under cooling with ice,  
25 followed by stirring for 10 minutes under cooling with ice. 367 mg of sulfamoyl chloride was added to this mixture, followed by stirring at room temperature for 3 hours. After water was added to the reaction mixture, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium  
30 sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 1:1 mixture of ethyl acetate and hexane as

the developing solvent) to obtain 106 mg of 2'-nitrobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 5.07(2H, br s), 7.30-8.00(8H, m).

$\text{MS}(\text{m/z})$ : 294( $\text{M}^+$ ), 215.

5

### Example 2

108 mg of 2'-nitrobiphenyl-4-ol was dissolved in 9.5 ml of methylene chloride, and 312 mg of 2,6-di-tert-butyl-4-methylpyridine and 347 mg of sulfamoyl chloride were successively added thereto under  
10 cooling with ice, followed by stirring at room temperature for 5 hours. After water was added to the reaction mixture, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 1:1  
15 mixture of ethyl acetate and hexane as the developing solvent) to obtain 149 mg of 2'-nitrobiphenyl-4-yl sulfamate.

### Example 3

The procedure of Example 1 was repeated, except that 27 mg  
20 of 4'-hydroxy-2-biphenylcarbonitrile was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 34 mg of 2'-cyanobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 5.02(2H, br s), 7.34-7.91(8H, m).

$\text{MS}(\text{m/z})$ : 274( $\text{M}^+$ ), 195.

### 25 Example 4

The procedure of Example 1 was repeated, except that 79 mg of 2'-fluorobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 81 mg of 2'-  
30 fluorobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.95(2H, br s), 7.00-7.71(8H, m).

MS(m/z): 267(M<sup>+</sup>), 188.

#### Example 5

The procedure of Example 1 was repeated, except that 45 mg  
5 of 2'-trifluoromethylbiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 24 mg of 2'-trifluoromethylbiphenyl-4-yl sulfamate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 4.96(2H, br s), 7.26-7.85(8H, m).

10 MS(m/z): 317(M<sup>+</sup>), 238.

#### Example 6

The procedure of Example 1 was repeated, except that 64 mg  
of 2'-methylbiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The  
15 resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 51 mg of 2'-methylbiphenyl-4-yl sulfamate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 2.26(3H, s), 4.97(2H, br s), 7.10-7.32(4H, m),  
7.37(4H, s).

20 MS(m/z): 263(M<sup>+</sup>), 184.

#### Example 7

The procedure of Example 2 was repeated, except that 37 mg  
of biphenyl-2,4'-diol was used in place of 2'-nitrobiphenyl-4-ol. The  
25 resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 17 mg of biphenyl-2,4'-diyl disulfamate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 7.14-7.68(8H, m).

MS(m/z): 344(M<sup>+</sup>), 265, 186.

Example 8

The procedure of Example 2 was repeated, except that 25 mg of 4'-hydroxy-2-biphenylacetonitrile was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 30 mg of 2'-cyanomethylbiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.64(2H, s), 7.15-7.63(8H, m).

$\text{MS}(\text{m/z})$ : 288( $\text{M}^+$ ), 209.

Example 9

The procedure of Example 1 was repeated, except that 79 mg of 3'-fluorobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 72 mg of 3'-fluorobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.94(2H, br s), 6.90-7.71(8H, m).

$\text{MS}(\text{m/z})$ : 267( $\text{M}^+$ ), 188.

Example 10

The procedure of Example 1 was repeated, except that 49 mg of 3'-nitrobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 40 mg of 3'-nitrobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.33-7.78(5H, m), 7.79-7.98(1H, m), 8.11-8.33(1H, m), 8.33-8.50(1H, m).

$\text{MS}(\text{m/z})$ : 294( $\text{M}^+$ ), 215.

Example 11

The procedure of Example 1 was repeated, except that 66 mg of 4'-hydroxy-3-biphenylcarbonitrile was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 55 mg of 3'-cyanobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 5.07(2H, br s), 7.34-8.06(8H, m).

$\text{MS}(\text{m/z})$ : 274( $\text{M}^+$ ), 195.

Example 12

The procedure of Example 1 was repeated, except that 40 mg of 4'-hydroxy-3-biphenylacetonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 15 mg of 3'-cyanomethylbiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 3.97(2H, s), 7.34-7.78(8H, m).

MS(m/z): 288( $\text{M}^+$ ), 209.

10 Example 13

The procedure of Example 1 was repeated, except that 125 mg of 4'-bromobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 123 mg of 15 4'-bromobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.33-7.71(8H, m).

MS(m/z): 329( $\text{M}^+ + 2$ ), 327( $\text{M}^+$ ), 249, 247.

Example 14

20 The procedure of Example 1 was repeated, except that 102 mg of 4'-chlorobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 111 mg of 4'-chlorobiphenyl-4-yl sulfamate.

25  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.99(2H, br s), 7.30-7.68(8H, m).

MS(m/z): 285( $\text{M}^+ + 2$ ), 283( $\text{M}^+$ ), 205, 203.

Example 15

30 The procedure of Example 1 was repeated, except that 100 mg of 4'-methoxybiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of

hexane and ethyl acetate as the developing solvent) to obtain 96 mg of 4'-methoxybiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.86(3H, s), 6.98 (2H, d,  $J=5.8\text{Hz}$ ), 7.35-7.67 (6H, m).

5      MS( $m/z$ ): 279( $\text{M}^+$ ), 199.

#### Example 16

The procedure of Example 1 was repeated, except that 108 mg of 4'-nitrobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. Thus, 10 there was obtained 108 mg of 4'-nitrobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.33-7.83(6H, m), 8.30(2H, d,  $J=6.0\text{Hz}$ ).

MS( $m/z$ ): 294( $\text{M}^+$ ), 215.

#### Example 17

15      The procedure of Example 1 was repeated, except that 228 mg of methyl 4'-hydroxy-4-biphenylcarboxylate was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 27 mg of methyl 4'-sulfamoyloxy-4-biphenylcarboxylate.

MS( $m/z$ ): 307( $\text{M}^+$ ), 227.

20

#### Example 18

The procedure of Example 1 was repeated, except that 500 mg of 4'-hydroxy-4-biphenylcarbonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 8:1 25 mixture of chloroform and ethyl acetate as the developing solvent) to obtain 489 mg of 4'-cyanobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 7.41(2H, d,  $J=5.5\text{Hz}$ ), 7.86(2H, d,  $J=5.5\text{Hz}$ ), 7.93(4H, s), 8.06(2H, br s).

MS( $m/z$ ): 274( $\text{M}^+$ ), 195.

30

#### Example 19

- The procedure of Example 1 was repeated, except that 50 mg of 4'-trifluoromethylbiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 35 mg of
- 5 4'-trifluoromethylbiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.96(2H, br s), 7.43(2H, d,  $J=6.0\text{Hz}$ ), 7.62(2H, d,  $J=6.0\text{Hz}$ ), 7.67(4H, s).

$\text{MS}(\text{m/z})$ : 317( $\text{M}^+$ ), 238.

10 Example 20

- The procedure of Example 1 was repeated, except that 13 mg of 4'-hydroxy-4-biphenylacetonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain
- 15 8 mg of 4'-cyanomethylbiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 3.93(2H, s), 7.24-7.82(8H, m).

$\text{MS}(\text{m/z})$ : 288( $\text{M}^+$ ), 209.

Example 21

- 20 The procedure of Example 1 was repeated, except that 50 mg of biphenyl-4,4'-diol was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 52 mg of biphenyl-4,4'-diyl disulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.42(4H, d,  $J=5.8\text{Hz}$ ), 7.66(4H, d,  $J=5.8\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 344( $\text{M}^+$ ), 265, 186.

25

Example 22

- The procedure of Example 1 was repeated, except that 23 mg of 2-nitrobiphenyl-4,4'-diol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1 mixture of
- 30 chloroform and methanol as the developing solvent) to obtain 9 mg of 2-nitrobiphenyl-4,4'-diyl disulfamate.



$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 6.97-7.43(7H, m).

$\text{MS}(\text{m/z})$ : 389( $\text{M}^+$ ), 310, 231.

### Example 23

5           The procedure of Example 1 was repeated, except that 48 mg of 2',4'-dinitrobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 5:1 mixture of chloroform and tetrahydrofuran as the developing solvent) to obtain 42 mg of 2',4'-dinitrobiphenyl-4-yl sulfamate.

10            $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.32-7.55(4H, m), 7.66(1H, d,  $J=5.3\text{Hz}$ ), 8.49(1H, dd,  $J=1.5, 5.3\text{Hz}$ ), 8.74(1H, d,  $J=1.5\text{Hz}$ ).  
 $\text{MS}(\text{m/z})$ : 339( $\text{M}^+$ ), 260.

### Example 24

15           The procedure of Example 1 was repeated, except that 55 mg of 2,2'-dinitrobiphenyl-4,4'-diol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 12 mg of 2,2'-dinitrobiphenyl-4,4'-diyl disulfamate.

20            $^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.48(2H, d,  $J=5.7\text{Hz}$ ), 7.73(2H, dd,  $J=1.7, 5.7\text{Hz}$ ), 8.19(2H, d,  $J=1.5\text{Hz}$ ).  
 $\text{MS}(\text{m/z})$ : 355( $\text{M}^+ - \text{SO}_2\text{NH}$ ), 276.

### Example 25

25           The procedure of Example 2 was repeated, except that 41 mg of 4'-hydroxy-4-nitro-2-biphenylcarbonitrile was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 40 mg of 2'-cyano-4'-nitrobiphenyl-4-yl sulfamate.

30            $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.40-7.73(4H, m), 7.74(1H, d,  $J=5.8\text{Hz}$ ), 8.51(1H, dd,  $J=1.5, 5.5\text{Hz}$ ), 8.65(1H, d,  $J=1.5\text{Hz}$ ).  
 $\text{MS}(\text{m/z})$ : 319( $\text{M}^+$ ), 240.

Example 26

The procedure of Example 2 was repeated, except that 132 mg of 4'-hydroxy-2-nitro-4-biphenylcarbonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 116 mg of 4'-cyano-2'-nitrobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.33-7.70(4H, m), 7.60(1H, d,  $J=5.3\text{Hz}$ ), 7.92(1H, dd,  $J=1, 5.3\text{Hz}$ ), 8.19(1H, d,  $J=1\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 319( $\text{M}^+$ ), 240.

10

Example 27

The procedure of Example 2 was repeated, except that 68 mg of 4'-hydroxy-2,4-biphenyldicarbonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 15:1 mixture of chloroform and methanol as the developing solvent) to obtain 44 mg of 2',4'-dicyanobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.39-7.78(4H, m), 7.76(1H, d,  $J=5.5\text{Hz}$ ), 8.06(1H, dd,  $J=1.7, 5.5\text{Hz}$ ), 8.28(1H, d,  $J=1.7\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 299( $\text{M}^+$ ), 220.

20

Example 28

The procedure of Example 1 was repeated, except that 90 mg of 4-[N-(4-hydroxybenzyl)amino]phenol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 6:1 mixture of chloroform and methanol as the developing solvent) to obtain 49 mg of 4-[N-sulfamoyl-N-(4-sulfamoyloxybenzyl)amino]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 4.77(2H, s), 7.0-8.1(14H, m).

$\text{SIMS}(\text{m/z})$ : 453( $\text{MH}^+$ ).

30

Example 29

The procedure of Example 1 was repeated, except that 22 mg of N-(4-hydroxybenzyl)-N-(4-hydroxyphenyl)methanesulfonamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 12 mg of 4-[N-methylsulfonyl-N-(4-sulfamoyloxybenzyl)amino]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 3.09(3H, s), 4.89(2H, s), 7.1-8.1(12H, m).

SIMS( $m/z$ ): 452( $\text{MH}^+$ ).

#### 10 Example 30

The procedure of Example 1 was repeated, except that 60 mg of N-(4-hydroxybenzyl)-N-(4-hydroxyphenyl)acetamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 61 mg of 4-[N-acetyl-N-(4-sulfamoyloxybenzyl)amino]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.90(3H, br s), 4.86(2H, s), 6.9-7.4(8H, m).

HR-SIMS( $m/z$ ): 416.0582( $\text{MH}^+$ ).

#### 20 Example 31

The procedure of Example 1 was repeated, except that 96 mg of 4-[N-acetyl-N-(4-hydroxybenzyl)amino]phenyl acetate was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 4:1 mixture of chloroform and acetone as the developing solvent) to obtain 57 mg of 4-[N-acetyl-N-(4-sulfamoyloxybenzyl)amino]phenyl acetate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.89(3H, br s), 2.28(3H, s), 4.85(2H, s), 6.9-7.4(8H, m).

MS( $m/z$ ): 378( $\text{M}^+$ ), 341, 151, 109, 107.

30

#### Example 32

The procedure of Example 1 was repeated, except that 200 mg of 4-hydroxy-N-(4-hydroxyphenyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was crystallized from chloroform to obtain 242 mg of 4-[N-(4-sulfamoyloxyphenyl)carbamoyl]-phenyl sulfamate.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 7.26(2H, d,  $J=9\text{Hz}$ ), 7.42(2H, d,  $J=9\text{Hz}$ ), 7.83(2H, d,  $J=9\text{Hz}$ ), 7.96(2H, d,  $J=9\text{Hz}$ ), 8.10(4H, br s), 10.35(1H, br s).

HR-SIMS( $m/z$ ): 388.0270( $\text{MH}^+$ ).

10

### Example 33

The procedure of Example 1 was repeated, except that 231 mg of N-ethyl-4-hydroxy-N-(4-hydroxyphenyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 242 mg of 4-[N-ethyl-N-(4-sulfamoyloxyphenyl)-carbamoyl]phenyl sulfamate.

15

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$ ): 1.23(3H, t,  $J=7\text{Hz}$ ), 3.94(2H, q,  $J=7\text{Hz}$ ), 6.9-7.4(8H, m).

20

MS( $m/z$ ): 415( $\text{M}^+$ ), 336, 119.

### Example 34

The procedure of Example 1 was repeated, except that 200 mg of 4-hydroxy-N-(4-hydroxyphenyl)-N-methylbenzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 5:1 mixture of chloroform and methanol as the developing solvent) to obtain 200 mg of 4-[N-methyl-N-(4-sulfamoyloxyphenyl)-carbamoyl]phenyl sulfamate.

25

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$ ): 3.48(3H, s), 6.9-7.4(8H, m).

30

ESI-MS( $m/z$ ): 402( $\text{MH}^+$ ).

Example 35

The procedure of Example 1 was repeated, except that 200 mg of 4-hydroxy-N-(3-hydroxyphenyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 5:1 mixture of chloroform and methanol as the developing solvent) to obtain 185 mg of 4-[N-(3-sulfamoyloxyphenyl)carbamoyl]-phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 6.9-8.2(12H, m), 10.44(1H, br s).

ESI-MS( $m/z$ ): 388( $\text{MH}^+$ ).

10

Example 36

The procedure of Example 1 was repeated, except that 222 mg of 4-hydroxy-N-(3-hydroxyphenyl)-N-methylbenzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 188 mg of 4-[N-methyl-N-(3-sulfamoyloxyphenyl)-carbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.51(3H, s), 6.7-8.5(8H, m).

ESI-MS( $m/z$ ): 402( $\text{MH}^+$ ).

20

Example 37

The procedure of Example 2 was repeated, except that 83 mg of N'-acetyl-4-hydroxy-N-phenylbenzohydrazide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was crystallized from ethyl acetate to obtain 53 mg of 4-(N'-acetyl-N-phenylhydrazino-carbonyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 1.90(3H, s), 7.1-7.7(9H, m).

MS( $m/z$ ): 270, 200, 150, 121.

30 Example 38

The procedure of Example 2 was repeated, except that 568 mg

of 4-[N-(4-hydroxybenzyl)-N-(1,2,4-triazol-4-yl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol, and 30 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by Silica gel column chromatography (using a 10:1 mixture of chloroform and methanol as the eluent) to obtain 512 mg of 4-[N-(4-cyano-phenyl)-N-(1,2,4-triazol-4-yl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 5.08(2H, s), 6.74(2H, d,  $J=9.2\text{Hz}$ ), 7.23(2H, d,  $J=8.8\text{Hz}$ ), 7.39(2H, d,  $J=8.8\text{Hz}$ ), 7.74(2H, d,  $J=9.0\text{Hz}$ ), 7.96(2H, br s), 8.80(2H, s).

10 MS( $m/z$ ): 291( $M^+ - \text{SO}_2\text{NH}$ ), 185.

#### Example 39

The procedure of Example 2 was repeated, except that 2.81 g of N-(4-cyanophenyl)-4-hydroxy-N-(1,2,4-triazol-4-yl)benzamide was used in place of 2'-nitrobiphenyl-4-ol, and 28 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by silica gel column chromatography (using a 10:1 mixture of chloroform and methanol as the eluent) to obtain 1.07 g of 4-[N-(4-cyanophenyl)-N-(1,2,4-triazol-4-yl)carbamoyl]phenyl sulfamate.

20  $^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 7.29(2H, d,  $J=8.8\text{Hz}$ ), 7.58(2H, d,  $J=8.8\text{Hz}$ ), 7.62 (2H, d,  $J=8.6\text{Hz}$ ), 7.90(2H, d,  $J=8.8\text{Hz}$ ), 8.13(2H, br s), 9.11 (2H, s).

MS( $m/z$ ): 384( $M^+$ ), 185.

#### 25 Example 40

32 mg of 4-formylphenyl sulfamate was added to a mixture composed of 11.5  $\mu\text{l}$  of aniline, 0.2 ml of ethanol, 27 mg of sodium acetate, 84  $\mu\text{l}$  of acetic acid, and 0.25 ml of water, and dissolved therein by heating. The resulting mixture was cooled with ice, and 20mg of sodium borohydride was slowly added thereto. After the reaction mixture was stirred at room temperature for 10 minutes, a saturated aqueous solu-

tion of sodium hydrogen carbonate was added thereto, and the product was extracted with ethyl acetate. After the organic layer was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was  
5 purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 27 mg of 4-(N-phenylaminomethyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.32(2H, s), 5.0(2H, br), 6.5-7.5(10H, m).

MS(m/z): 278( $\text{M}^+$ ), 199.

10

#### Example 41

The procedure of Example 40 was repeated, except that 15 mg of 4-aminobenzonitrile was used in place of aniline. Thus, there was obtained 16 mg of 4-[N-(4-cyanophenyl)aminomethyl]phenyl sulfamate.

15  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.37(2H, s), 6.1(1H, br), 6.58(2H, d,  $J=8.8\text{Hz}$ ), 7.2-7.5(6H, m).

MS(m/z): 303( $\text{M}^+$ ), 224.

#### Example 42

20 The procedure of Example 40 was repeated, except that 15 mg of 2-aminobenzonitrile was used in place of aniline. Thus, there was obtained 5 mg of 4-[N-(2-cyanophenyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.44(2H, d,  $J=5.7\text{Hz}$ ), 5.0(3H, br), 6.60(1H, br d,  $J=7.7\text{Hz}$ ), 6.74(1H, dd,  $J=1.0, 7.7\text{Hz}$ ), 7.0-8.0(6H, m).

25 MS(m/z): 303( $\text{M}^+$ ), 224.

#### Example 43

The procedure of Example 40 was repeated, except that 27.5 mg of 4-aminophenol was used in place of aniline. Thus, there was  
30 obtained 27 mg of 4-[N-(4-hydroxyphenyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.24(2H, s), 6.4-7.5(8H, m).

MS(m/z): 294( $\text{M}^+$ ), 215.

#### Example 44

5           The procedure of Example 40 was repeated, except that 34.8 mg of 4-nitroaniline was used in place of aniline. Thus, there was obtained 7 mg of 4-[N-(4-nitrophenyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.43(2H, s), 6.56(2H, d,  $J=9.2\text{Hz}$ ), 7.31(4H, s), 8.05(2H, d,  $J=9.2\text{Hz}$ ).

10          MS(m/z): 323( $\text{M}^+$ ), 244.

#### Example 45

15           The procedure of Example 2 was repeated, except that 66 mg of 4-[N-(4-hydroxybenzyl)-N-(4-methoxyphenyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol, and 2.9 ml of N,N-dimethylformamide was used in place of methylene chloride. Thus, there was obtained 47 mg of 4-[N-(4-cyanophenyl)-N-(4-methoxyphenyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.82(3H, s), 4.8-5.1(4H, m), 6.5-7.5(12H, m).

20          MS(m/z): 409( $\text{M}^+$ ), 330.

#### Example 46

25           The procedure of Example 2 was repeated, except that 60 mg of 4-[N-(4-hydroxybenzyl)-N-phenylamino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol, and 2.9 ml of N,N-dimethylformamide was used in place of methylene chloride. Thus, there was obtained 51 mg of 4-[N-(4-cyanophenyl)-N-phenylaminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.8-5.1(4H, m), 6.5-7.5(13H, m).

MS(m/z): 379( $\text{M}^+$ ), 300.

30

#### Example 47



The procedure of Example 2 was repeated, except that 33 mg of N-(4-hydroxybenzyl)-4,4'-iminobisbenzonitrile was used in place of 2'-nitrobiphenyl-4-ol, and 1.45 ml of N,N-dimethylformamide was used in place of methylene chloride. Thus, there was obtained 18 mg of 4-[N,N-bis(4-cyanophenyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.9-5.2(4H, m), 7.14(4H, d,  $J=9\text{Hz}$ ), 7.28(4H, s), 7.54(4H, d,  $J=8.8\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 404( $\text{M}^+$ ), 325.

#### 10 Example 48

The procedure of Example 2 was repeated, except that 11 mg of 4-[N-(4-hydroxybenzyl)-N-(4-pyridyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 5 mg of 4-[N-(4-cyanophenyl)-N-(4-pyridyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 5.06(2H, s), 6.83(2H, dd,  $J=1.5, 5.1\text{Hz}$ ), 7.28(4H, s), 7.32(2H, d,  $J=8.1\text{Hz}$ ), 7.66(2H, d,  $J=8.8\text{Hz}$ ), 8.26(2H, dd,  $J=1.3, 5.1\text{Hz}$ ).

20  $\text{MS}(\text{m/z})$ : 301( $\text{M}^+ - \text{SO}_2\text{NH}$ ), 195.

#### Example 49

The procedure of Example 2 was repeated, except that 50 mg of 4-(N-phenylaminomethyl)phenol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 21 mg of 4-(N-phenyl-N-sulfamoylaminomethyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3 + \text{CD}_3\text{OD}, \delta)$ : 4.79(2H, s), 7.2-7.4(9H, m).

$\text{MS}(\text{m/z})$ : 357( $\text{M}^+$ ), 278.

30

#### Example 50

The procedure of Example 2 was repeated, except that 56 mg of 4-[N-(4-hydroxybenzyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 18 mg of 4-[N-(4-cyanophenyl)-N-sulfamoylamino-methyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.86(4H, s), 4.37(2H, s), 6.58(2H, d,  $J=8.8\text{Hz}$ ), 7.2-7.5(6H, m).

MS(m/z): 303( $\text{M}^+-\text{SO}_2\text{NH}$ ), 224.

10

#### Example 51

The procedure of Example 1 was repeated, except that 83 mg of N-(4-cyanophenyl)-N-(4-hydroxybenzyl)nicotinamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and acetone as the developing solvent) to obtain 19 mg of 4-[N-(4-cyanophenyl)-N-nicotinoylamino-methyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 5.19(2H, s), 7.1-7.5(7H, m), 7.6-7.8(3H, m), 7.93(2H, br s), 8.4-8.6(2H, m).

MS(m/z): 329 ( $\text{M}^+-\text{SO}_2\text{NH}$ ), 223.

20

#### Example 52

The procedure of Example 2 was repeated, except that 78 mg of N-(4-cyanophenyl)-N-(4-hydroxybenzyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and acetone as the developing solvent) to obtain 45 mg of 4-[N-benzoyl-N-(4-cyanophenyl)amino-methyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 4.93(2H, s), 7.1-7.9(13H, m), 8.0-8.2(2H, m).

MS(m/z): 328( $\text{M}^+-\text{SO}_2\text{NH}$ ), 223.

30

Example 53

The procedure of Example 2 was repeated, except that 89 mg of 4-cyano-N-(4-cyanophenyl)-N-(4-hydroxybenzyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified  
5 by TLC (using a 19:1 mixture of chloroform and acetone as the developing solvent) to obtain 16 mg of 4-[N-(4-cyanobenzoyl)-N-(4-cyanophenyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 4.94(2H, s), 7.1-7.8(10H, m), 8.07(2H, d,  $J=8.6\text{Hz}$ ), 8.22(2H, d,  $J=8.4\text{Hz}$ ).

10  $\text{MS}(\text{m/z})$ : 353( $\text{M}^+ - \text{SO}_2\text{NH}$ ), 236.

Example 54

The procedure of Example 1 was repeated, except that 73 mg of 4-hydroxy-N,N-diphenylbenzamide was used in place of 2'-nitro-  
15 biphenyl-4-ol. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 50 mg of 4-(N,N-diphenylcarbamoyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 7.0-7.6(14H, m), 8.04(2H, br s).

$\text{MS}(\text{m/z})$ : 368( $\text{M}^+$ ), 289.

20

Example 55

The procedure of Example 2 was repeated, except that 534 mg of N-benzyl-4-hydroxybenzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by silica gel column  
25 chromatography (using a 10:1 mixture of chloroform and methanol as the eluent) to obtain 204 mg of 4-(N-benzylcarbamoyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.61(2H, d,  $J=5.7\text{Hz}$ ), 7.0-7.5(10H, m), 7.81(2H, d,  $J=8.6\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 306( $\text{M}^+$ ), 227.

30

### Example 56

The procedure of Example 1 was repeated, except that 54 mg of 4-hydroxy-N-phenylbenzamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 40 mg of 4-(N-phenylcarbamoyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$ : 7.0-7.5(5H, m), 7.76(2H, d,  $J=7.9\text{Hz}$ ), 7.9-8.2(4H, m), 10.26(1H, br s).

$\text{MS}(\text{m/z})$ : 292( $\text{M}^+$ ), 213.

10

### Example 57

The procedure of Example 2 was repeated, except that 45 mg of 4-cyano-N-(4-hydroxybenzyl)-N-methylbenzamide was used in place of 2'-nitrobiphenyl-4-ol, and 1.5 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 4:1 mixture of chloroform and acetone as the developing solvent) to obtain 5 mg of 4-[N-(4-cyanobenzoyl)-N-methylaminomethyl]-phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.73-3.20(3H, m), 4.3-4.8 (2H, br), 5.30(2H, s), 7.0-7.4(4H, m), 7.53(2H, d,  $J=8.4\text{Hz}$ ), 7.71(2H, d,  $J=8.3\text{Hz}$ ).

20

$\text{MS}(\text{m/z})$ : 345( $\text{M}^+$ ), 266.

### Example 58

The procedure of Example 40 was repeated, except that 32 mg of 4-amino-1,2,4-triazole was used in place of aniline. The resulting crude product was purified by TLC (using a 4:1 mixture of chloroform and methanol as the developing solvent) to obtain 39 mg of 4-[N-(1,2,4-triazol-4-yl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 4.10(2H, s), 6.71(2H, d,  $J=8.6\text{Hz}$ ), 7.06(2H, d,  $J=8.6\text{Hz}$ ), 8.27(2H, s).

30

Example 59

The procedure of Example 2 was repeated, except that 26 mg of 3-cyano-N-(4-hydroxybenzyl)-N-(1,2,4-triazol-4-yl)benzamide was used in place of 2'-nitrobiphenyl-4-ol, and 0.5 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 7:1 mixture of chloroform and methanol as the developing solvent) to obtain 10 mg of 4-[N-(3-cyanobenzoyl)-N-(1,2,4-triazol-4-yl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 5.60(2H, s), 7.16-8.06(8H, m), 8.16-8.27

(2H, m), 9.24(1H, s), 10.90(1H, s).

MS(m/z): 399(MH $^+$ ).

Example 60

The procedure of Example 2 was repeated, except that 71 mg of 4-[N-(4-hydroxybenzyl)-N-(3-pyridyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol, and 1.8 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 52 mg of 4-[N-(4-cyanophenyl)-N-(3-pyridyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 5.12(2H, s), 6.87(2H, d, J=5.8Hz), 7.12-7.97 (8H, m), 8.41(1H, dd, J=1.2, 3.0Hz), 8.59(1H, d, J=1.7Hz).

MS(m/z): 301(M $^+$ -SO $_2$ NH).

Example 61

The procedure of Example 2 was repeated, except that 38 mg of 4-[N-(4-hydroxybenzyl)-N-methylamino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol, and 1.2 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 19 mg of 4-[N-(4-cyanophenyl)-N-methyl-

aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 3.15(3H, s), 4.67(2H, s), 6.80(2H, d,  $J=7.8\text{Hz}$ ),  
7.26(4H, s), 7.44(2H, d,  $J=7.8\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 317( $\text{M}^+$ ), 238( $\text{M}^+ - \text{SO}_2\text{NH}$ ).

5

### Example 62

The procedure of Example 2 was repeated, except that 24 mg of 4-[N-ethyl-N-(4-hydroxybenzyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol, and 0.7 ml of N,N-dimethylformamide was used in  
10 place of methylene chloride. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 13 mg of 4-[N-(4-cyanophenyl)-N-ethyl-aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 1.23(3H, t,  $J=4.5\text{Hz}$ ), 3.59(2H, q,  $J=4.7\text{Hz}$ ),  
15 4.64(2H, s), 6.76(2H, d,  $J=5.8\text{Hz}$ ), 7.25(4H, s), 7.40(2H, d,  $J=5.8\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 331( $\text{M}^+$ ), 252 ( $\text{M}^+ - \text{SO}_2\text{NH}$ ).

### Example 63

The procedure of Example 2 was repeated, except that 37 mg  
20 of N-(4-cyanophenyl)-N-(4-hydroxybenzyl)-2-thiophenecarboxamide was used in place of 2'-nitrobiphenyl-4-ol, and 0.9 ml of 1,2-dichloroethane was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 17 mg of 4-[N-(4-cyanophenyl)-N-(2-  
25 thienylcarbonyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 5.05(2H, d,  $J=2.2\text{Hz}$ ), 5.22(2H, br s), 6.70-7.72 (11H, m).

$\text{MS}(\text{m/z})$ : 413( $\text{M}^+$ ), 334( $\text{M}^+ - \text{SO}_2\text{NH}$ ).

### 30 Example 64

The procedure of Example 2 was repeated, except that 43 mg

of N-(4-cyanophenyl)-N-(4-hydroxybenzyl)-3-thiophenecarboxamide was used in place of 2'-nitrobiphenyl-4-ol, and 1.0 ml of 1,2-dichloroethane was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 23 mg of 4-[N-(4-cyanophenyl)-N-(3-thienylcarbonyl)aminomethyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 5.16(2H, s), 6.74-7.77(11H, m).

MS(m/z): 334( $\text{M}^+$ - $\text{SO}_2\text{NH}$ ).

#### 10 Example 65

The procedure of Example 2 was repeated, except that 83 mg of N-(4-cyanophenyl)-4-hydroxybenzamide was used in place of 2'-nitrobiphenyl-4-ol, and 2.6 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 13:1 mixture of chloroform and methanol as the developing solvent) to obtain 8 mg of 4-[N-(4-cyanophenyl)carbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 6.87(2H, d,  $J=5.8\text{Hz}$ ), 7.56-8.00(6H, m).

MS(m/z): 238( $\text{M}^+$ - $\text{SO}_2\text{NH}$ ).

20

#### Example 66

The procedure of Example 2 was repeated, except that 279 mg of N-(4-cyanophenyl)-4-hydroxy-N-methylbenzamide was used in place of 2'-nitrobiphenyl-4-ol, and 8.4 ml of N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 13:1 mixture of chloroform and methanol as the developing solvent) to obtain 143 mg of 4-[N-(4-cyanophenyl)-N-methylcarbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 3.50(3H, s), 7.08-7.49(6H, m), 7.63(2H, d,  $J=6.0\text{Hz}$ ).

MS(m/z): 331( $\text{M}^+$ ), 252( $\text{M}^+$ - $\text{SO}_2\text{NH}$ ).

30

Example 67

The procedure of Example 2 was repeated, except that 24 mg of N,N'-dimethyl-4-hydroxybenzohydrazide was used in place of 2'-nitro-biphenyl-4-ol. The resulting crude product was purified by TLC (using a  
 5 7:1 mixture of chloroform and methanol as the developing solvent) to obtain 2 mg of 4-(N',N'-dimethylhydrazinocarbonyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 2.65(6H, s), 7.39(2H, d,  $J=5.5\text{Hz}$ ), 7.83(2H, d,  $J=5.7\text{Hz}$ ).

MS(m/z): 259( $\text{M}^+$ ).

10

Example 68

The procedure of Example 2 was repeated, except that 23 mg of 2-hydroxy-N-(4-hydroxyphenyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol, and 1.5 ml of N,N-dimethylformamide was used in  
 15 place of methylene chloride. Thus, there was obtained 21 mg of 2-[N-(4-sulfamoyloxyphenyl)carbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 6.7-8.4(12H, m), 10.49(1H, br s).

MS(m/z): 308( $\text{M}^+ - \text{SO}_2\text{NH}$ ), 229.

20 Example 69

The procedure of Example 2 was repeated, except that 23 mg of 3-hydroxy-N-(2-hydroxyphenyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol, and 1.5 ml of N,N-dimethylformamide was used in  
 25 place of methylene chloride. Thus, there was obtained 26 mg of 3-[N-(2-sulfamoyloxyphenyl)carbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 7.3-8.3(13H, m).

MS(m/z): 290( $\text{M}^+ - \text{HOSO}_2\text{NH}_2$ ), 211.

Example 70

30 The procedure of Example 2 was repeated, except that 23 mg of 3-hydroxy-N-(3-hydroxyphenyl)benzamide was used in place of 2'-



nitrobiphenyl-4-ol, and 1.5 ml of N,N-dimethylformamide was used in place of methylene chloride. Thus, there was obtained 25 mg of 3-[N-(3-sulfamoyloxyphenyl)carbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 6.9-8.1(12H, m), 10.48(1H, br s).

5       $\text{MS}(\text{m/z})$ : 290( $\text{M}^+ - \text{HOSO}_2\text{NH}_2$ ).

#### Example 71

The procedure of Example 2 was repeated, except that 23 mg of 3-hydroxy-N-(4-hydroxyphenyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol, and 1.5 ml of N,N-dimethylformamide was used in place of methylene chloride. Thus, there was obtained 33 mg of 3-[N-(4-sulfamoyloxyphenyl)carbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 7.1-8.1(12H, m), 10.41(1H, br s).

$\text{MS}(\text{m/z})$ : 290( $\text{M}^+ - \text{HOSO}_2\text{NH}_2$ ), 229.

15

#### Example 72

The procedure of Example 2 was repeated, except that 23 mg of 4-hydroxy-N-(2-hydroxyphenyl)benzamide was used in place of 2'-nitrobiphenyl-4-ol, and 1.5 ml of N,N-dimethylformamide was used in place of methylene chloride. Thus, there was obtained 18 mg of 4-[N-(2-sulfamoyloxyphenyl)carbamoyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 7.3-8.5(12H, m).

$\text{MS}(\text{m/z})$ : 290( $\text{M}^+ - \text{HOSO}_2\text{NH}_2$ ), 211.

#### 25      Example 73

The procedure of Example 2 was repeated, except that 271 mg of 4-[N-(4-hydroxybenzyl)-N-(2-pyrazinyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 211 mg of 4-[N-(4-cyanophenyl)-N-(2-pyrazinyl)aminomethyl]phenyl sulfamate.

30

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 5.32(2H, s), 7.19(2H, d,  $J=5.5\text{Hz}$ ), 7.35(2H, d,  $J=6.0\text{Hz}$ ), 7.53(2H, d,  $J=6.0\text{Hz}$ ), 7.77(2H, d,  $J=5.5\text{Hz}$ ), 7.83-8.39 (3H, m).

MS( $m/z$ ): 302( $M^+ - \text{SO}_2\text{NH}$ ).

5

#### Example 74

The procedure of Example 1 was repeated, except that 118 mg of 4-[N-(4-hydroxybenzyl)-N-(2-thenyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified  
10 by TLC (using a 10:1 mixture of chloroform and tetrahydrofuran as the developing solvent) to obtain 4-[N-(4-cyanophenyl)-N-(2-thenyl)amino-methyl]phenyl sulfamate.

$^1\text{H-NMR}$ ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 4.75(2H, s), 4.89(2H, s), 6.73-7.54(11H, m).

MS( $m/z$ ): 320( $M^+ - \text{SO}_2\text{NH}$ ).

15

#### Example 75

The procedure of Example 1 was repeated, except that 88 mg of 4-[N-(4-hydroxybenzyl)-N-(3-thenyl)amino]benzonitrile was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified  
20 by TLC (using a 10:1 mixture of chloroform and tetrahydrofuran as the developing solvent) to obtain 4-[N-(4-cyanophenyl)-N-(3-thenyl)amino-methyl]phenyl sulfamate.

$^1\text{H-NMR}$ ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 4.74(4H, s), 6.69-7.51(11H, m).

MS( $m/z$ ): 399( $M^+$ ), 320( $M^+ - \text{SO}_2\text{NH}$ ).

25

#### Example 76

A mixture composed of 215 mg of 2'-nitrobiphenyl-4-ol and 1 ml of toluene was cooled with ice, and 148 mg of chlorosulfonyl isocyanate was added dropwise thereto, followed by refluxing for 17 hours. After  
30 water was added to the reaction mixture under cooling with ice, the product was extracted with ethyl acetate. The organic layer was washed

with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 160 mg of 2'-nitrobiphenyl-4-yl sulfamate.

5

#### Example 77

The procedure of Example 1 was repeated, except that 88 mg of 4-(1-naphthyl)phenol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of  
10 hexane and ethyl acetate as the developing solvent) to obtain 63 mg of 4-(1-naphthyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.99(2H, br s), 7.28-7.66(8H, m), 7.66-8.03  
(3H, m).

MS(m/z): 299( $\text{M}^+$ ), 220.

15

#### Example 78

The procedure of Example 1 was repeated, except that 98 mg of 2-hydroxy-9-fluorenone was used in place of 2'-nitrobiphenyl-4-ol. Thus, there was obtained 55 mg of 9-oxofluoren-2-yl sulfamate.

20  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.22-7.77(7H, m).

MS(m/z): 275( $\text{M}^+$ ), 196.

#### Example 79

The procedure of Example 1 was repeated, except that 36 mg  
25 of fluoren-2-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 1:1 mixture of diethyl ether and hexane as the developing solvent) to obtain 22 mg of fluoren-2-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.91(2H, s), 7.13-7.91(7H, m).

30 MS(m/z): 261( $\text{M}^+$ ), 181.

Example 80

The procedure of Example 1 was repeated, except that 33 mg of 4-(3-pyridyl)phenol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1 mixture of  
5 chloroform and methanol as the developing solvent) to obtain 4-(3-pyridyl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.32-7.85(4H, m), 7.97-8.19(1H, m), 8.53(1H, dd,  $J=1.2, 3.2\text{Hz}$ ), 8.80(1H, d,  $J=1.5\text{Hz}$ ).

MS(m/z): 250( $\text{M}^+$ ), 171.

10

Example 81

The procedure of Example 1 was repeated, except that 102 mg of 4-(2-methylthiazol-4-yl)phenol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1  
15 mixture of chloroform and methanol as the developing solvent) to obtain 14 mg of 4-(2-methylthiazol-4-yl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.77(3H, s), 7.31(1H, s), 7.35(2H, d,  $J=6\text{Hz}$ ), 7.85(2H, d,  $J=5.7\text{Hz}$ ).

MS(m/z): 270( $\text{M}^+$ ), 190.

20

Example 82

The procedure of Example 1 was repeated, except that 52 mg of 4-(2-aminothiazol-4-yl)phenol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1  
25 mixture of chloroform and methanol as the developing solvent) to obtain 8 mg of 4-(2-sulfamoylaminothiazol-4-yl)phenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 6.96(1H, s), 7.30(2H, d,  $J=5.7\text{Hz}$ ), 7.86(2H, d,  $J=5.7\text{Hz}$ ), 8.21(1H, s).

MS(m/z): 350( $\text{M}^+$ ), 270, 192.

30

Example 83

The procedure of Example 1 was repeated, except that 23 mg of 5-(4-hydroxyphenyl)-N-methyl-3-isoxazolecarboxamide was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 8 mg of 4-[3-(N-methylcarbamoyl)isoxazol-5-yl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 2.94(3H, s), 7.07(1H, s), 7.48(2H, d,  $J=5.7\text{Hz}$ ), 7.93(2H, d,  $J=5.7\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 297( $\text{M}^+$ ), 218.

10

#### Example 84

The procedure of Example 1 was repeated, except that 102 mg of 3-chlorobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 68 mg of 3-chlorobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 5.07(2H, br s), 7.30-7.76(8H, m).

$\text{MS}(\text{m/z})$ : 285( $\text{M}^++2$ ), 283( $\text{M}^+$ ), 206, 204.

#### 20 Example 85

The procedure of Example 1 was repeated, except that 25 mg of 3-bromobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 1:1 mixture of diethyl ether and hexane as the developing solvent) to obtain 17 mg of 3-bromobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.30-7.80(8H, m).

$\text{MS}(\text{m/z})$ : 329( $\text{M}^++2$ ), 327( $\text{M}^+$ ), 249.

#### Example 86

30 The procedure of Example 1 was repeated, except that 30 mg of 3-iodobiphenyl-4-ol was used in place of 2'-nitrobiphenyl-4-ol. The

resulting crude product was purified by TLC (using a 1:1 mixture of diethyl ether and hexane as the developing solvent) to obtain 10 mg of 3-iodobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 5.12(2H, br s), 7.30-7.70(8H, m).

5       $\text{MS}(\text{m/z})$ : 375( $\text{M}^+$ ), 296.

#### Example 87

The procedure of Example 1 was repeated, except that 228 mg of N-(4-hydroxybiphenyl-3-yl)acetamide was used in place of 2'-nitro-  
10 biphenyl-4-ol. Thus, there was obtained 92 mg of 3-(N-acetyl)amino-biphenyl-3-yl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.22(3H, s), 7.31-7.67(8H, m), 8.40(1H, br s).

$\text{MS}(\text{m/z})$ : 306( $\text{M}^+$ ), 227, 185.

#### 15      Example 88

20 mg of N-(4'-hydroxybiphenyl-4-yl)methanesulfonamide was dissolved in 0.2 ml of N,N-dimethylformamide, and 11  $\mu\text{l}$  of triethylamine was added thereto under cooling with ice, followed by stirring for 30 minutes under cooling with ice. 35 mg of sulfamoyl chloride was added  
20 to this mixture, followed by stirring at room temperature for 3 hours. After the reaction mixture was poured into a saturated aqueous solution of sodium chloride, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting  
25 crude product was purified by TLC (using a 1:1 mixture of acetone and hexane as the developing solvent) to obtain 23 mg of 4'-(N-methyl-sulfonyl)aminobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{DMSO}-d_6, \delta)$ : 3.01(3H, s), 7.30(2H, d,  $J=7.8\text{Hz}$ ), 7.34(2H, d,  $J=7.8\text{Hz}$ ), 7.63(2H, d,  $J=7.8\text{Hz}$ ), 7.69(2H, d,  $J=7.8\text{Hz}$ ), 7.98(2H, s),  
30 9.83(1H, s).

$\text{MS}(\text{m/z})$ : 342( $\text{M}^+$ ), 184.

Example 89

The procedure of Example 88 was repeated, except that 105 mg of N-(4'-hydroxybiphenyl-2-yl)methanesulfonamide was used in place of N-(4'-hydroxybiphenyl-4-yl)methanesulfonamide. The resulting crude  
5 product was purified by TLC (using a 6:1 mixture of chloroform and acetone as the developing solvent) to obtain 111 mg of 2'-(N-methylsulfonyl)aminobiphenyl-4-yl sulfamate.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 2.74(3H, s), 7.34(2H, d, J=8.6Hz), 7.3-7.5(4H, m), 7.53(2H, d, J=8.6Hz), 8.03(2H, s), 8.95(1H, s).

10 MS(m/z): 342(M<sup>+</sup>), 263, 184.

Example 90

The procedure of Example 88 was repeated, except that 129 mg of 4'-hydroxybiphenyl-4-yl methanesulfonate was used in place of N-(4'-  
15 hydroxybiphenyl-4-yl)methanesulfonamide. The resulting crude product was purified by TLC (using a 1:1 mixture of acetone and hexane as the developing solvent) to obtain 133 mg of 4'-methylsulfonyloxy-biphenyl-4-yl sulfamate.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 3.40(3H, s), 7.3-7.4(2H, m), 7.4-7.5(2H, m),  
20 7.7-7.8(4H, m), 8.01(2H, s).

MS(m/z): 343(M<sup>+</sup>), 264, 185.

Example 91

The procedure of Example 2 was repeated, except that 100 mg  
25 of (2Z)-3-(4-hydroxyphenyl)-2-phenylprop-2-enenitrile was used in place of 2'-nitrobiphenyl-4-ol, and 1,2-dichloroethane was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 15:1 mixture of chloroform and methanol as the developing solvent) to obtain 109 mg of 4-[(1Z)-2-cyano-2-phenylvinyl]phenyl  
30 sulfamate.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD, δ): 7.3-7.9(6H, m), 7.77(2H, d, J=9.0Hz), 7.98(2H,

d,  $J=9.0\text{Hz}$ ).

MS( $m/z$ ): 300( $M^+$ ), 221.

### Example 92

5           The procedure of Example 2 was repeated, except that 122 mg of (2Z)-2,3-bis(4-hydroxyphenyl)prop-2-enenitrile was used in place of 2'-nitrobiphenyl-4-ol, and 1,2-dichloroethane was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 3:1 mixture of chloroform and acetone as the developing  
10 solvent) to obtain 86 mg of 4-[(1Z)-2-(4-sulfamoyloxyphenyl)-1-cyano-vinyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.46(2H, d,  $J=8.5\text{Hz}$ ), 7.49(2H, d,  $J=8.5\text{Hz}$ ), 7.7-7.9(3H, m), 8.02(2H, d,  $J=9.0\text{Hz}$ ).

MS( $m/z$ ): 316( $M^+-79$ ), 237.

15

### Example 93

          The procedure of Example 2 was repeated, except that 100 mg of (2Z)-2-(4-hydroxybenzyl)-3-phenylprop-2-enenitrile was used in place of 2'-nitrobiphenyl-4-ol, and 1,2-dichloroethane was used in place of  
20 methylene chloride. The resulting crude product was purified by TLC (using a 15:1 mixture of chloroform and methanol as the developing solvent) to obtain 104 mg of 4-[(1Z)-1-cyano-2-phenylvinyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.3-7.6(5H, m), 7.6-8.1(5H, m).

25           MS( $m/z$ ): 300( $M^+$ ), 221.

### Example 94

          The procedure of Example 2 was repeated, except that 81 mg of 4-[N-(4-hydroxybenzyl)-N-(2-pyrimidyl)amino]benzonitrile was used in  
30 place of 2'-nitrobiphenyl-4-ol, and N,N-dimethylformamide was used in place of methylene chloride. The resulting crude product was purified



by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 22 mg of 4-[N-(4-cyanophenyl)-N-(2-pyrimidyl)aminomethyl]phenyl sulfamate.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 5.27(2H, br s), 7.27(4H, d, J=3.8Hz), 7.4-7.8  
5 (2H, m), 7.8-8.1(3H, m), 8.2-8.8(2H, m).

MS(m/z): 302(M<sup>+</sup>-79), 195, 107.

#### Example 95

The procedure of Example 88 was repeated, except that 120 mg  
10 of 4'-hydroxy-4-nitro-2-biphenylcarbonitrile was used in place of N-(4'-hydroxybiphenyl-4-yl)methanesulfonamide, and 0.430 ml of N,N-dimethylsulfamoyl chloride was used in place of sulfamoyl chloride. The resulting crude product was purified by TLC (using a 16:1 mixture of chloroform and acetone as the developing solvent) to obtain 97 mg of 2'-  
15 cyano-4'-nitrobiphenyl-4-yl N,N-dimethylsulfamate.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 2.97(6H, s), 7.5-7.6(2H, m), 7.7-7.8(2H, m),  
7.94(1H, d, J=8.8Hz), 8.57(1H, dd, J=2.2, 8.3Hz), 8.84(1H, d,  
J=2.2Hz).

MS(m/z): 347(M<sup>+</sup>), 240, 108.

20

#### Example 96

43 mg of 4'-aminobiphenyl-4-ol was dissolved in 0.7 ml of N,N-dimethylacetamide, and 107 mg of sulfamoyl chloride was added thereto under cooling with ice, followed by stirring at room temperature for 2.4  
25 hours. After the reaction mixture was poured into a saturated aqueous solution of sodium chloride, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 17:10 mixture of  
30 chloroform and tetrahydrofuran as the developing solvent) to obtain 42 mg of 4'-(sulfamoylamino)biphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.30(2H, d,  $J=8.7\text{Hz}$ ), 7.37(2H, d,  $J=8.7\text{Hz}$ ),  
7.56(2H, d,  $J=8.7\text{Hz}$ ), 7.63(2H, d,  $J=8.7\text{Hz}$ ).  
MS( $m/z$ ): 343( $\text{M}^+$ ), 264, 184.

#### 5 Example 97

The procedure of Example 96 was repeated, except that 75 mg of 2'-aminobiphenyl-4-ol was used in place of 4'-aminobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 17:10 mixture of chloroform and tetrahydrofuran as the developing solvent) to obtain 36  
10 mg of 2'-(sulfamoylamino)biphenyl-4-yl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.1-7.5(3H, m), 7.41(2H, d,  $J=8.6\text{Hz}$ ), 7.51(2H, d,  $J=8.6\text{Hz}$ ), 7.66(1H, dd,  $J=0.8, 7.9\text{Hz}$ ).  
MS( $m/z$ ): 343( $\text{M}^+$ ), 264, 184.

#### 15 Example 98

The procedure of Example 96 was repeated, except that 12 mg of (2Z)-2-[4-(N-sulfamoylamino)phenyl]-3-(4-hydroxyphenyl)prop-2-ene-nitrile was used in place of 4'-aminobiphenyl-4-ol. The resulting crude product was purified by TLC (using a 2:1 mixture of chloroform and  
20 acetone as the developing solvent) to obtain 5 mg of 4-[(1Z)-2-[4-(N-sulfamoylamino)phenyl]-2-cyanovinyl]phenyl sulfamate.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 7.16(2H, d,  $J=8.6\text{Hz}$ ), 7.31(2H, d,  $J=8.6\text{Hz}$ ),  
7.67(2H, d,  $J=8.6\text{Hz}$ ), 7.74(1H, s), 7.97(2H, d,  $J=8.6\text{Hz}$ ).  
MS( $m/z$ ): 315( $\text{M}^+-79$ ), 236.

25

#### Example 99

The procedure of Example 96 was repeated, except that 279 mg of methyl 4-[(1Z)-2-cyano-2-(4-hydroxyphenyl)vinyl]phenylcarboxylate was used in place of 4'-aminobiphenyl-4-ol. The resulting crude product  
30 was purified by TLC (using a 8:1 mixture of chloroform and tetrahydrofuran as the developing solvent) to obtain 284 mg of methyl 4-[(1Z)-2-(4-

sulfamoyloxyphenyl)-2-cyanovinyl]phenylcarboxylate.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 3.89(3H, s), 7.44(2H, d,  $J=8.8\text{Hz}$ ), 7.88(2H, d,  $J=8.8\text{Hz}$ ), 8.05(2H, d,  $J=8.4\text{Hz}$ ), 8.1(4H, m), 8.14(1H, s).

MS( $m/z$ ): 358( $M^+$ ), 279, 248.

5

#### Example 100

262 mg of 2'-cyano-4'-nitrobiphenyl-4-yl sulfamate was dissolved in 2.5 ml of formic acid, and 445 mg of 10% palladium-carbon was added thereto, followed by stirring at room temperature for 5 minutes. After the reaction mixture was filtered to remove any insoluble matter and the filtrate was poured into a saturated aqueous solution of sodium chloride, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 52 mg of 4'-amino-2'-cyanobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 5.73(2H, br s), 6.93(1H, dd,  $J=2.4, 8.4\text{Hz}$ ), 6.98(1H, d,  $J=2.4\text{Hz}$ ), 7.27(1H, d,  $J=8.4\text{Hz}$ ), 7.36(2H, d,  $J=8.4\text{Hz}$ ), 7.55(2H, d,  $J=8.4\text{Hz}$ ), 8.10(2H, s).

20

MS( $m/z$ ): 289( $M^+$ ), 210.

#### Example 101

The procedure of Example 100 was repeated, except that 101 mg of 4'-cyano-2'-nitrobiphenyl-4-yl sulfamate was used in place of 2'-cyano-4'-nitrobiphenyl-4-yl sulfamate. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 15 mg of 2'-amino-4'-cyanobiphenyl-4-yl sulfamate.

$^1\text{H-NMR}$ ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 7.01(1H, dd,  $J=1.5, 7.7\text{Hz}$ ), 7.08(1H, d,  $J=1.5\text{Hz}$ ), 7.15(1H, d,  $J=7.7\text{Hz}$ ), 7.43(2H, d,  $J=8.7\text{Hz}$ ), 7.48(2H, d,

30

$J=8.7\text{Hz}$ ).

MS( $m/z$ ): 289( $M^+$ ), 210.

#### Preparation Example 1

- 5           A mixture composed of 392 mg of 2-bromophenylacetonitrile, 334 mg of 4-methoxyphenylboronic acid, 0.9 mg of palladium acetate, 691 mg of potassium acetate, 645 mg of tetrabutylammonium bromide, and 2.2 ml of distilled water was stirred at 70°C for 2 hours under an atmosphere of nitrogen. After the reaction mixture was poured into a
- 10 saturated aqueous solution of sodium chloride, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting crude product was purified by silica gel column chromatography (using a 3:1 mixture of hexane and ethyl acetate as the
- 15 eluent) to obtain 343 mg of 4'-methoxy-2-biphenylaceto-nitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.62(2H, s), 3.86(3H, s), 6.86-7.70(8H, m).

MS( $m/z$ ): 223( $M^+$ ).

#### Preparation Example 2

- 20           89 mg of 4'-methoxy-2-biphenylacetonitrile was dissolved in 0.66 ml of methylene chloride, and 0.8 ml of a 1 M solution of boron tribromide in methylene chloride was added thereto under cooling with ice, followed by stirring for 40 minutes. This mixture was returned to room temperature and stirred for an additional 40 minutes. After the
- 25 reaction mixture was poured into a saturated aqueous solution of sodium chloride, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as
- 30 the developing solvent) to obtain 43 mg of 4'-hydroxy-2-biphenylaceto-nitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.62(2H, s), 6.73-7.64(8H, m).

$\text{MS}(\text{m/z})$ : 209( $\text{M}^+$ ).

### Preparation Example 3

- 5           The procedure of Preparation Example 1 was repeated, except that 365 mg of 2-chloro-5-nitrobenzonitrile was used in place of 2-bromophenylacetonitrile. The resulting crude product was purified by silica gel column chromatography (using a 2:1 mixture of chloroform and hexane as the eluent) to obtain 428 mg of 4'-methoxy-4-nitro-2-
- 10 biphenylcarbonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.89(3H, s), 7.07(2H, d,  $J=5.5\text{Hz}$ ), 7.55(2H, d,  $J=5.8\text{Hz}$ ), 7.67(1H, d,  $J=6.0\text{Hz}$ ), 8.43(1H, dd,  $J=1.7, 5.5\text{Hz}$ ), 8.60(1H, d,  $J=1.5\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 254( $\text{M}^+$ ).

15

### Preparation Example 4

- The procedure of Preparation Example 2 was repeated, except that 102 mg of 4'-methoxy-4-nitro-2-biphenylcarbonitrile was used in place of 4'-methoxy-2-biphenylacetonitrile. The resulting crude product
- 20 was purified by TLC (using a 3:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 87 mg of 4'-hydroxy-4-nitro-2-biphenylcarbonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 6.99(2H, d,  $J=5.8\text{Hz}$ ), 7.49(2H, d,  $J=5.3\text{Hz}$ ), 7.68(1H, d,  $J=5.8\text{Hz}$ ), 8.44(1H, dd,  $J=1.7, 5.3\text{Hz}$ ), 8.60(1H, d,  $J=1.5\text{Hz}$ ).

25

$\text{MS}(\text{m/z})$ : 240( $\text{M}^+$ ).

### Preparation Example 5

- The procedure of Preparation Example 1 was repeated, except
- 30 that 548 mg of 4-chloro-3-nitrobenzonitrile was used in place of 2-bromophenylacetonitrile. The resulting crude product was purified by silica

gel column chromatography (using a 2:1 mixture of chloroform and hexane as the eluent) to obtain 640 mg of 4'-methoxy-2-nitro-4-biphenylcarbonitrile.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 3.86(3H, s), 6.98(2H, d, J=5.7Hz), 7.24(2H, d, J=5.7Hz), 7.58(1H, d, J=5.3Hz), 7.83(1H, dd, J=1.2, 5.3Hz), 8.06(1H, d, J=1.2Hz).

MS(m/z): 254(M<sup>+</sup>).

#### Preparation Example 6

The procedure of Preparation Example 2 was repeated, except that 208 mg of 4'-methoxy-2-nitro-4-biphenylcarbonitrile was used in place of 4'-methoxy-2-biphenylacetoneitrile. The resulting crude product was purified by TLC (using a 3:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 140 mg of 4'-hydroxy-2-nitro-4-biphenylcarbonitrile.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 6.91(2H, d, J=6.0Hz), 7.16(2H, d, J=5.3Hz), 7.59(1H, d, J=5.3Hz), 7.85(1H, dd, J=0.8, 5.3Hz), 8.07(1H, d, J=0.8Hz).

MS(m/z): 240(M<sup>+</sup>).

#### Preparation Example 7

A mixture composed of 15 g of 4-benzyloxybenzyl chloride and 15 g of 4-aminophenol was refluxed in 200 ml of N,N-dimethylformamide for 30 minutes. After water was added to the reaction mixture, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After the solvent was distilled off, the resulting crude product was purified by silica gel column chromatography (using a 50:1 mixture of chloroform and acetone as the eluent) to obtain 11 g of 4-[N-(4-benzyloxybenzyl)-amino]phenol.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 4.19(2H, s), 5.05(3H, s), 6.4-7.5(13H, m).

MS(m/z): 305(M<sup>+</sup>), 197, 91.

#### Preparation Example 8

500 mg of 4-[N-(4-benzyloxybenzyl)amino]phenol was dissolved  
 5 in 4 ml of pyridine, and 1 ml of methanesulfonyl chloride was added  
 thereto under cooling with ice, followed by stirring for 30 minutes. After  
 water was added to the reaction mixture, the precipitated crystals were  
 separated by filtration to obtain 719 mg of 4-[N-(4-benzyloxybenzyl)-N-  
 methylsulfonylamino]phenyl methanesulfonate.

10 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 2.93(3H, s), 3.13(3H, s), 4.77(2H, s), 5.02(2H, s),  
 6.7-7.5 (13H, m).

MS(m/z): 197, 91.

#### Preparation Example 9

15 A mixture composed of 350 mg of 4-[N-(4-benzyloxybenzyl)-N-  
 methylsulfonylamino]phenyl methanesulfonate, 350 mg of 10%  
 palladium-carbon, and 10 ml of dioxane was stirred for 2 days under an  
 atmospheric pressure of hydrogen. The reaction mixture was filtered to  
 remove any insoluble matter, and the solvent was distilled off from the  
 20 filtrate. Thus, there was obtained 260 mg of 4-[N-(4-hydroxybenzyl)-N-  
 methylsulfonylamino]phenyl methanesulfonate.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 2.94(3H, s), 3.15(3H, s), 4.73(2H, s), 6.72(2H, d,  
 J=9Hz), 7.06(2H, d, J=9Hz), 7.25(4H, s).

MS(m/z): 371(M<sup>+</sup>), 265, 186, 107.

25

#### Preparation Example 10

A mixture composed of 80 mg of 4-[N-(4-hydroxybenzyl)-N-  
 methylsulfonylamino]phenyl methanesulfonate and 0.5 ml of a 28%  
 methanolic solution of sodium methoxide was stirred in 2 ml of methanol  
 30 and 1 ml of tetrahydrofuran at 50°C for 1 hour. After hydrochloric acid  
 was added to the reaction mixture, the product was extracted with ethyl

- acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 38 mg of
- 5 N-(4-hydroxybenzyl)-N-(4-hydroxyphenyl)methanesulfonamide.
- $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.91(3H, s), 4.66(2H, s), 6.6-7.2(8H, m).
- MS(m/z): 293( $\text{M}^+$ ), 212, 187, 108.

#### Preparation Example 11

- 10 100 mg of 4-[N-(4-benzyloxybenzyl)amino]phenol was dissolved in 4 ml of pyridine, and 2 ml of acetic anhydride was added thereto, followed by stirring at room temperature for 2 hours. After water was added to the reaction mixture, the product was extracted with ethyl acetate. The organic layer was washed with 5% hydrochloric acid and a
- 15 saturated aqueous solution of sodium hydrogen carbonate, and dried over anhydrous sodium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using chloroform as the developing solvent) to obtain 114 mg of 4-[N-acetyl-N-(4-benzyloxybenzyl)amino]phenyl acetate.
- 20  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.87(3H, s), 2.29(3H, s), 4.79(2H, s), 5.03(2H, s), 6.7-7.5(13H, m).
- MS(m/z): 389( $\text{M}^+$ ), 197, 91.

#### Preparation Example 12

- 25 The procedure of Preparation Example 9 was repeated, except that 400 mg of 4-[N-acetyl-N-(4-benzyloxybenzyl)amino]phenyl acetate was used in place of 4-[N-(4-benzyloxybenzyl)-N-methylsulfonylamino]phenyl methanesulfonate, and 6 ml of ethanol was used in place of dioxane. Thus, there was obtained 270 mg of 4-[N-acetyl-N-(4-hydroxy-
- 30 benzyl)amino]phenyl acetate.



$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.88(3H, s), 2.29(3H, s), 4.78(2H, s), 6.6-7.3 (8H, m).

MS(m/z): 299( $\text{M}^+$ ), 193, 151, 109, 107.

### 5 Preparation Example 13

The procedure of Preparation Example 10 was repeated, except that 45 mg of 4-[N-acetyl-N-(4-hydroxybenzyl)amino]phenyl acetate was used in place of 4-[N-(4-hydroxybenzyl)-N-methylsulfonyl-amino]phenyl methanesulfonate. Thus, there was obtained 20 mg of N-(4-hydroxybenzyl)-N-(4-hydroxyphenyl)acetamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.84(3H, s), 4.72(2H, s), 6.70(2H, d,  $J=9\text{Hz}$ ), 6.74(4H, s), 6.98(2H, d,  $J=9\text{Hz}$ ).

MS(m/z): 257( $\text{M}^+$ ), 151, 109.

### 15 Preparation Example 14

A mixture composed of 600 mg of 4-methoxy-N-(4-methoxyphenyl)benzamide and 150 mg of 60% sodium hydride was stirred in 7.5 ml of dimethyl sulfoxide at 50°C for 10 minutes. Then, 1.05 ml of ethyl iodide was added, and the reaction mixture was stirred for 30 minutes. After water was added to the reaction mixture, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 80:1 mixture of chloroform and acetone as the developing solvent) to obtain 591 mg of N-ethyl-4-methoxy-N-(4-methoxyphenyl)benzamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.19(3H, t,  $J=7\text{Hz}$ ), 3.73(3H, s), 3.75(3H, s), 3.90(2H, q,  $J=7\text{Hz}$ ), 6.5-7.4(8H, m).

MS(m/z): 285( $\text{M}^+$ ), 135.

### 30 Preparation Example 15

The procedure of Preparation Example 2 was repeated, except

that 585 mg of N-ethyl-4-methoxy-N-(4-methoxyphenyl)benzamide was used in place of 4'-methoxy-2-biphenylacetonitrile. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 466 mg of N-ethyl-4-hydroxy-N-(4-hydroxyphenyl)benzamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.17(3H, t,  $J=7\text{Hz}$ ), 3.87(2H, q,  $J=7\text{Hz}$ ), 6.4-7.3(8H, m).

$\text{MS}(\text{m/z})$ : 257( $\text{M}^+$ ), 137, 121.

#### 10 Preparation Example 16

The procedure of Preparation Example 14 was repeated, except that 1.2 ml of methyl iodide was used in place of ethyl iodide. Thus, there was obtained 629 mg of 4-methoxy-N-(4-methoxyphenyl)-N-methylbenzamide.

15  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.43(3H, s), 3.74(3H, s), 3.75(3H, s), 6.5-7.3 (8H, m).

$\text{MS}(\text{m/z})$ : 271( $\text{M}^+$ ), 135.

#### Preparation Example 17

20 The procedure of Preparation Example 2 was repeated, except that 603 mg of 4-methoxy-N-(4-methoxyphenyl)-N-methylbenzamide was used in place of 4'-methoxy-2-biphenylacetonitrile. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 489 mg of 4-hydroxy-N-(4-hydroxyphenyl)-N-methylbenzamide.

25  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.40(3H, s), 6.4-7.3(8H, m).

$\text{MS}(\text{m/z})$ : 243( $\text{M}^+$ ), 123, 121.

#### Preparation Example 18

30 The procedure of Preparation Example 14 was repeated, except that 4-methoxy-N-(3-methoxyphenyl)benzamide was used in place

of 4-methoxy-N-(4-methoxyphenyl)benzamide, and 1.2 ml of methyl iodide was used in place of ethyl iodide. Thus, there was obtained 625 mg of 4-methoxy-N-(3-methoxyphenyl)-N-methylbenzamide.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 3.46(3H, s), 3.69(3H, s), 3.74(3H, s), 6.5-7.4  
5 (8H, m).

MS(m/z): 271(M<sup>+</sup>), 135.

#### Preparation Example 19

The procedure of Preparation Example 2 was repeated, except  
10 that 618 mg of 4-methoxy-N-(3-methoxyphenyl)-N-methylbenzamide was used in place of 4'-methoxy-2-biphenylacetonitrile. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 442 mg of 4-hydroxy-N-(3-hydroxyphenyl)-N-methylbenzamide.

15 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 3.42(3H, s), 6.4-7.3(8H, m).

MS(m/z): 243 (M<sup>+</sup>), 123, 121.

#### Preparation Example 20

1.08 g of phenylhydrazine was dissolved in 10 ml of pyridine,  
20 and 0.78 g of acetic anhydride was added thereto under cooling with ice, followed by stirring for 20 minutes. Then, 2.0 g of 4-methoxybenzoyl chloride was added thereto, followed by stirring at room temperature for 15 hours. After water was added to the reaction mixture, the product was extracted with ethyl acetate. The organic layer was washed with 5%  
25 hydrochloric acid and a 5% aqueous solution of sodium hydroxide, and dried over anhydrous sodium sulfate. After the solvent was distilled off, the resulting crude product was purified by silica gel column chromatography (using a 40:1 mixture of chloroform and methanol as the eluent) to obtain 1.0 g of N'-acetyl-4-methoxy-N-phenylbenzohydrazide.

30 <sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 2.07(3H, s), 3.76(3H, s), 6.72(2H, d, J=9Hz), 7.21 (5H, s), 7.43(2H, d, J=9Hz), 8.09(1H, br s).

10019693, 010302

MS(m/z): 284(M<sup>+</sup>), 135.

#### Preparation Example 21

The procedure of Preparation Example 2 was repeated, except  
5 that 500 mg of N'-acetyl-4-methoxy-N-phenylbenzohydrazide was used in  
place of 4'-methoxy-2-biphenylacetonitrile. The resulting crude product  
was purified by TLC (using a 15:1 mixture of chloroform and methanol as  
the developing solvent) to obtain 224 mg of N'-acetyl-4-hydroxy-N-  
phenylbenzohydrazide.

10 <sup>1</sup>H-NMR(CDCl<sub>3</sub>+CD<sub>3</sub>OD, δ): 2.04(3H, s), 6.66(2H, d, J=9Hz), 7.21  
(5H, s), 7.35(2H, d, J=9Hz).

MS(m/z): 270(M<sup>+</sup>), 121.

#### Preparation Example 22

15 A mixture composed of 167 mg of 4-(tert-butyldimethyl-  
silyloxy)benzylalcohol and 1 ml of thionyl chloride was heated under  
reflux for 1 hour. After the thionyl chloride was distilled off from the  
reaction mixture under reduced pressure, its azeotropic distillation with  
toluene was carried out three times to remove any thionyl chloride. The  
20 resulting residue was dissolved in 4.3 ml of acetonitrile, and 108 mg of 4-  
[N-(1,2,4-triazol-4-yl)amino]benzonitrile and 172 mg of potassium  
carbonate were added thereto, followed by stirring at room temperature  
for 18 hours. After water was added to the reaction mixture and  
neutralized with dilute hydrochloric acid, the product was extracted with  
25 ethyl acetate. After the extract was washed with water and dried over  
anhydrous sodium sulfate, the solvent was distilled off under reduced  
pressure. The resulting crude product was purified by silica gel column  
chromatography (using a 9:1 mixture of chloroform and methanol as the  
eluent) to obtain 102 mg of 4-[N-(4-hydroxybenzyl)-N-(1,2,4-triazol-4-yl)-  
30 amino]benzonitrile.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 4.89(2H, s), 6.6-6.8(4H, m), 7.04(2H, d,  $J=8.6\text{Hz}$ ), 7.72(2H, d,  $J=9.0\text{Hz}$ ), 8.65(2H, s), 9.40(1H, s).  
 MS( $m/z$ ): 291( $M^+$ ), 185.

### 5 Preparation Example 23

A mixture composed of 10.43 g of 4-[N- (1,2,4-triazol-4-yl)-amino]benzonitrile, 7.9 ml of triethylamine, and 56 ml of methylene chloride was stirred under cooling with ice, and a mixture composed of 23.7 g of 4-(trimethylsilyloxy)benzoyl chloride and 28 ml of methylene chloride was added dropwise thereto, followed by stirring at room temperature for 1 hour. Dilute hydrochloric acid was added to the reaction mixture, followed by stirring at room temperature overnight. After the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogen carbonate, the product was extracted with tetrahydrofuran-diethyl ether (1:1). After the extract was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was purified by silica gel column chromatography (using a 4:1 mixture of chloroform and acetone as the eluent) to obtain 6.2 g of N-(4-cyanophenyl)-4-hydroxy-N-(1,2,4-triazol-4-yl)benzamide.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 6.71(2H, d,  $J=8.8\text{Hz}$ ), 7.38(2H, d,  $J=8.8\text{Hz}$ ), 7.46(2H, d,  $J=8.8\text{Hz}$ ), 7.86(2H, d,  $J=8.8\text{Hz}$ ), 9.05(2H, s), 10.21 (1H, br s).

MS( $m/z$ ): 305( $M^+$ ), 185.

25

### Preparation Example 24

The procedure of Example 1 was repeated, except that 244 mg of 4-hydroxybenzaldehyde was used in place of 2'-nitrobiphenyl-4-ol. The resulting crude product was purified by silica gel column chromatography (using a 19:1 mixture of chloroform and acetone as the eluent) to obtain 203 mg of 4-formylphenyl sulfamate.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 7.50(2H, d,  $J=8.6\text{Hz}$ ), 7.94(2H, d,  $J=9.0\text{Hz}$ ),  
10.00(1H, s).  
 $\text{MS}(\text{m/z})$ : 201( $\text{M}^+$ ), 121.

#### 5 Preparation Example 25

A mixture composed of 286 mg of 4-(*tert*-butyldimethylsilyloxy)benzyl alcohol and 1.75 ml of thionyl chloride was heated under reflux for 1 hour. After the thionyl chloride was distilled off from the reaction mixture under reduced pressure, its azeotropic distillation with  
10 toluene was carried out three times to remove any thionyl chloride. Thus, there was obtained 4-(*tert*-butyldimethylsilyloxy)benzyl chloride.

224 mg of 4-[N-(4-methoxyphenyl)amino]benzonitrile was dissolved in 1.2 ml of N,N-dimethylformamide, and 48 mg of sodium borohydride was added thereto under cooling with ice, followed by  
15 stirring at room temperature for 30 minutes. The previously prepared 4-(*t*-butyldimethylsilyloxy)benzyl chloride was dissolved in 1.2 ml of N,N-dimethylformamide and added to the reaction mixture under cooling with ice, followed by stirring at room temperature for 2 days. After water was added to the reaction mixture, the product was extracted with  
20 ethyl acetate. After the extract was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in 1.2 ml of tetrahydrofuran, and 1.2 ml of a 1 M tetrahydrofuran solution of tetrabutylammonium fluoride was added thereto, followed by stirring at  
25 room temperature for 15 minutes. After a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, the product was extracted with ethyl acetate. After the extract was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was  
30 purified by silica gel column chromatography (using ethyl acetate as the eluent) to obtain 229 mg of 4-[N-(4-hydroxybenzyl)-N-(4-methoxyphenyl)]

amino]benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.82(3H, s), 4.7-5.0(3H, m), 6.4-7.4(12H, m).

$\text{MS}(\text{m/z})$ : 330( $\text{M}^+$ ), 224.

#### 5 Preparation Example 26

The procedure of Preparation Example 25 was repeated, except that 194 mg of 4-(N-phenylamino)benzonitrile was used in place of 4-[N-(4-methoxyphenyl)amino]benzonitrile. Thus, there was obtained 172 mg of 4-[N-(4-hydroxybenzyl)-N-phenylamino]benzonitrile.

10  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.9(2H, br s), 5.1-6.4(1H, br), 6.7-7.9(13H, m).

$\text{MS}(\text{m/z})$ : 300( $\text{M}^+$ ), 194.

#### Preparation Example 27

The procedure of Preparation Example 22 was repeated, except that 219 mg of 4,4'-iminobisbenzonitrile was used in place of 4-[N-(1,2,4-triazol-4-yl)amino]benzonitrile. The resulting crude product was purified by silica gel column chromatography (using a 7:1 mixture of hexane and ethyl acetate as the eluent) to obtain 95 mg of N-[4-(tert-butyltrimethylsilyloxy)benzyl]-4,4'-iminobisbenzonitrile.

20 Then, 92 mg of N-[4-(tert-butyltrimethylsilyloxy)benzyl]-4,4'-iminobisbenzonitrile was dissolved in 0.21 ml of tetrahydrofuran, and 0.21 ml of a 1 M tetrahydrofuran solution of tetrabutylammonium fluoride was added thereto, followed by stirring at room temperature for 30 minutes. After a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, the product was extracted with ethyl acetate. After the extract was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was purified by TLC (using a 39:1 mixture of chloroform and acetone as the developing solvent) to obtain 54 mg of N-(4-hydroxybenzyl)-4,4'-iminobisbenzonitrile.

25  
30

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.8-5.1(3H, m), 6.7-7.6(12H, m).

$\text{MS}(\text{m/z})$ : 325( $\text{M}^+$ ), 219.

#### Preparation Example 28

5           900 mg of metallic potassium was mixed with 40 ml of tert-butanol under an atmosphere of nitrogen, and this mixture was heated under reflux to form a homogeneous solution. After the solvent was distilled off from the reaction mixture under an atmosphere of nitrogen, its azeotropic distillation with toluene was carried out twice. The  
10 resulting residue was dried under reduced pressure to prepare potassium tert-butoxide.

10 ml of dimethyl sulfoxide was added to the above potassium tert-butoxide, followed by cooling in an ice-water bath. While this mixture was kept at 20°C or below, 1.882 g of 4-aminopyridine was added  
15 thereto, followed by stirring at room temperature for 1 hour. 1.21 g of 4-fluorobenzonitrile was dissolved in 3 ml of dimethyl sulfoxide, and this solution was added dropwise to the above reaction mixture kept at an internal temperature of 30°C or below, followed by stirring at room temperature for 30 minutes. After water was added to the reaction  
20 mixture, the resulting mixture was acidified with dilute hydrochloric acid and then neutralized with a saturated aqueous solution of sodium hydrogen carbonate. The product was extracted with tetrahydrofuran-diethyl ether (1:1), and the organic layer was washed with water and dried over anhydrous sodium sulfate. After the solvent was distilled off,  
25 the resulting crude product was purified by silica gel column chromatography (using a 9:1 mixture of chloroform and methanol as the eluent) to obtain 1.85 g of 4-[N-(4-pyridyl)amino]benzo-nitrile.

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$ : 7.0-7.2(2H, m), 7.30(2H, d,  $J=8.1\text{Hz}$ ), 7.71(2H, d,  $J=8.8\text{Hz}$ ), 7.9-8.1(2H, m).

30            $\text{MS}(\text{m/z})$ : 195( $\text{M}^+$ ).



Preparation Example 29

The procedure of Preparation Example 22 was repeated, except that 114 mg of 4-[N-(4-pyridyl)amino]benzonitrile was used in place of 4-[N-(1,2,4-triazol-4-yl)amino]benzonitrile. The resulting crude  
 5 product was purified by TLC (using a 9:1 mixture of chloroform and methanol as the developing solvent) to obtain 48 mg of 4-[N-[4-(tert-butyl-  
 butyldimethylsilyloxy)benzyl]-N-(4-pyridyl)amino]benzonitrile.

Then, 31 mg of 4-[N-[4-(tert-butyl-  
 (4-pyridyl)amino]benzonitrile was dissolved in 0.33 ml of tetrahydro-  
 10 furan, and 0.15 ml of a 1 M tetrahydrofuran solution of tetrabutyl-  
 ammonium fluoride was added thereto, followed by stirring at room  
 temperature for 45 minutes. After water was added to the reaction  
 mixture, the product was extracted with tetrahydrofuran-diethyl ether  
 (1:1). After the extract was washed with water and dried over anhydrous  
 15 sodium sulfate, the solvent was distilled off under reduced pressure.  
 The resulting crude product was purified by TLC (using a 9:1 mixture of  
 chloroform and methanol as the developing solvent) to obtain 14 mg of 4-  
 [N-(4-hydroxybenzyl)-N-(4-pyridyl)amino]benzonitrile.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 4.96(2H, s), 6.7-6.9(4H, m), 7.03(2H, d, J=8.8Hz),  
 20 7.33(2H, d, J=8.3 Hz), 7.63(2H, d, J=9.0 Hz), 8.22(2H, br d,  
 J=6.4 Hz).

MS(m/z): 301(M<sup>+</sup>), 195.

Preparation Example 30

25 The procedure of Example 40 was repeated, except that 3.58 g  
 of 4-aminobenzonitrile was used in place of aniline, and 4.62 g of 4-  
 hydroxybenzaldehyde was used in place of 4-formylphenyl sulfamate.  
 The resulting crude product was purified by silica gel column chromato-  
 graphy (using a 39:1 mixture of chloroform and acetone as the eluent) to  
 30 obtain 3.37 g of 4-[N-(4-hydroxybenzyl)amino]-benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.25(2H, s), 6.59(2H, d,  $J=9.0\text{Hz}$ ), 6.82(2H, d,  $J=8.6\text{Hz}$ ), 7.16(2H, d,  $J=8.6\text{Hz}$ ), 7.40(2H, d,  $J=8.8\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 224( $\text{M}^+$ ), 118.

#### 5 Preparation Example 31

224 mg of 4-[N-(4-hydroxybenzyl)amino]benzonitrile, 0.28 ml of triethylamine, and 7 ml of tetrahydrofuran were mixed, and 178 mg of nicotinoyl chloride hydrochloride was slowly added thereto, followed by stirring at room temperature overnight. After water was added to the  
10 reaction mixture, the product was extracted with tetrahydrofuran-diethyl ether (1:1). After the extract was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was purified by TLC (using a 9:1 mixture of chloroform and acetone as the developing  
15 solvent) to obtain 292 mg of N-(4-cyanophenyl)-N-(4-hydroxybenzyl)-nicotinamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.2-4.7(3H, m), 6.61(2H, d,  $J=8.8\text{Hz}$ ), 7.1-7.7 (7H, m), 8.44(1H, dt,  $J=2.0, 8.0\text{Hz}$ ), 8.86(1H, dd,  $J=1.8, 4.8\text{Hz}$ ), 9.39(1H, d,  $J=1.5\text{Hz}$ ).

20  $\text{MS}(\text{m/z})$ : 329( $\text{M}^+$ ), 223.

#### Preparation Example 32

Reaction was carried out in the same manner as in Preparation Example 31, except that 0.116 ml of benzoyl chloride was used in place of  
25 nicotinoyl chloride hydrochloride. The resulting crude product was purified by TLC (using chloroform as the developing solvent) to obtain 337 mg of N-(4-cyanophenyl)-N-(4-hydroxybenzyl)benzamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.39(2H, s), 4.5(1H, br), 6.61(2H, d,  $J=9\text{Hz}$ ), 7.1-7.7(9H, m), 8.19(2H, dd,  $J=1.8, 7.9\text{Hz}$ ).

30  $\text{MS}(\text{m/z})$ : 328( $\text{M}^+$ ).

### Preparation Example 33

Reaction was carried out in the same manner as in Preparation Example 31, except that 166 mg of 4-cyanobenzoyl chloride was used in place of nicotinoyl chloride hydrochloride. The resulting crude product  
5 was purified by TLC (using chloroform as the developing solvent) to obtain 344 mg of 4-cyano-N-(4-cyanophenyl)-N-(4-hydroxybenzyl)benzamide.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 4.39(2H, d,  $J=5.9\text{Hz}$ ), 6.68(2H, d,  $J=8.8\text{Hz}$ ),  
6.8-8.0(7H, m), 8.09(2H, d,  $J=8.1\text{Hz}$ ), 8.25(2H, d,  $J=8.4\text{Hz}$ ).

10  $\text{MS}(m/z)$ : 353( $\text{M}^+$ ), 247.

### Preparation Example 34

825 mg of 4-cyanobenzoyl chloride was dissolved in 9 ml of dichloroethane, and mixed with 0.69 ml of 4-methoxybenzylamine and  
15 1.57 ml of triethylamine, followed by stirring for 2.5 hours. Thereafter, the reaction was stopped by the addition of 1 ml of distilled water. After the product was extracted with chloroform, the extract was successively washed with 2 N hydrochloric acid, a saturated aqueous solution of sodium hydrogen carbonate, and a saturated aqueous solution of sodium  
20 chloride, and dried over anhydrous sodium sulfate. After the solvent was distilled off, the resulting crude product was purified by silica gel column chromatography (using a 20:1 mixture of chloroform and acetone as the eluent) to obtain 1.29 g of 4-cyano-N-(4-methoxy-benzyl) benzamide.

25  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$ ): 3.80(3H, s), 4.55(2H, d,  $J=6.0\text{Hz}$ ), 6.2-6.5(1H, br), 6.88(2H, d,  $J=8.6\text{Hz}$ ), 7.27(2H, d,  $J=8.8\text{Hz}$ ), 7.60-8.05(4H, m).

$\text{MS}(m/z)$ : 266( $\text{M}^+$ ), 235.

### Preparation Example 35

30 79 mg of 4-cyano-N-(4-methoxybenzyl)benzamide was dissolved in 2.5 ml of tetrahydrofuran, and 24 mg of 60% sodium hydride was

added thereto, followed by heating under reflux for 5 minutes in an atmosphere of nitrogen. After cooling, 0.1 ml of methyl iodide was added thereto, followed by stirring for 15 minutes. Thereafter, the reaction was stopped by the addition of 1 ml of distilled water. After the product was extracted with ethyl acetate, the extract was successively washed with 2 N hydrochloric acid, a saturated aqueous solution of sodium hydrogen carbonate, and a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. After the solvent was distilled off, the resulting crude product was purified by TLC (using a 1:1 mixture of ethyl acetate and hexane as the developing solvent) to obtain 72 mg of 4-cyano-N-(4-methoxybenzyl)-N-methylbenzamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.68-3.17(3H, m), 3.81(3H, s), 4.30-4.80(2H, m), 6.88(2H, d,  $J=8.6\text{Hz}$ ), 7.0-7.4(2H, m), 7.51(2H, d,  $J=6.4\text{Hz}$ ), 7.70(2H, d,  $J=8.4\text{Hz}$ ).

MS( $m/z$ ): 280( $\text{M}^+$ ), 265.

#### Preparation Example 36

The procedure of Preparation Example 2 was repeated, except that 71 mg of 4-cyano-N-(4-methoxybenzyl)-N-methylbenzamide was used in place of 4'-methoxy-2-biphenylacetonitrile, and toluene was used in place of methylene chloride. The resulting crude product was purified by TLC (using a 4:1 mixture of chloroform and acetone as the developing solvent) to obtain 53 mg of 4-cyano-N-(4-hydroxybenzyl)-N-methylbenzamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.68-3.20(3H, m), 4.20-4.77(2H, m), 6.80(2H, d,  $J=8.6\text{Hz}$ ), 6.9-7.4(2H, m), 7.51(2H, d,  $J=8.6\text{Hz}$ ), 7.70(2H, d,  $J=8.6\text{Hz}$ ).

MS( $m/z$ ): 266( $\text{M}^+$ ), 251.

#### Preparation Example 37

The procedure of Preparation Example 34 was repeated, except that 101 mg of 4-[N-(1,2,4-triazol-4-yl)aminomethyl]phenol was

used in place of 4-methoxybenzylamine, and 105 mg of 3-cyanobenzoyl chloride was used in place of 4-cyanobenzoyl chloride. The resulting crude product was purified by TLC (using a 10:1 mixture of chloroform and methanol as the developing solvent) to obtain 26 mg of 3-cyano-N-(4-hydroxybenzyl)-N-(1,2,4-triazol-4-yl)benzamide.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 4.97(2H, s), 6.47 and 7.01(2H,  $J_{\text{AB}}=6.8$  Hz), 8.41(2H, s).

$\text{MS}(\text{m/z})$ : 319( $\text{M}^+$ ), 251.

#### 10 Preparation Example 38

190 mg of 4-[N-(3-pyridyl)amino]benzonitrile was dissolved in 5 ml of N,N-dimethylformamide, and 44 mg of 60% sodium hydride was added thereto under cooling with ice, followed by stirring at 40-50°C for 30 minutes. Then, 273 mg of 4-benzyloxybenzyl chloride was added to the reaction mixture under cooling with ice, followed by stirring at room temperature for 2 hours. After the reaction mixture was poured into water, the product was extracted with chloroform. After the extract was washed with water and dried over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was purified by TLC (using a 1:1 mixture of ethyl acetate and hexane as the developing solvent) to obtain 234 mg of 4-[N-(4-benzyloxybenzyl)-N-(3-pyridyl)amino]benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.93(2H, s), 5.03(2H, s), 6.67-7.63(15H, m), 8.44(1H, dd,  $J=1.2, 3.0\text{Hz}$ ), 8.54(1H, d,  $J=1.5\text{Hz}$ ).

$\text{MS}(\text{m/z})$ : 391( $\text{M}^+$ ).

#### Preparation Example 39

The procedure of Preparation Example 9 was repeated, except that 222 mg of 4-[N-(4-benzyloxybenzyl)-N-(3-pyridyl)amino]benzonitrile was used in place of 4-[N-(4-benzyloxybenzyl)-N-methylsulfonylamino]-phenyl methanesulfonate, and 3 ml of ethyl acetate was used in place of

dioxane. The resulting mixture was stirred for 3 days under an atmospheric pressure of hydrogen. The reaction mixture was filtered to remove any insoluble matter, and the solvent was distilled off from the filtrate. The resulting crude product was purified by TLC (using a 1:1  
5 mixture of ethyl acetate and hexane as the developing solvent) to obtain 95 mg of 4-[N-(4-hydroxybenzyl)-N-(3-pyridyl)amino]benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.92(2H, s), 6.58-7.70(10H, m), 8.39(1H, dd,  $J=1.2, 3.2\text{Hz}$ ), 8.48(1H, d,  $J=1.5\text{Hz}$ ).

MS(m/z): 301( $\text{M}^+$ ).

10

#### Preparation Example 40

The procedure of Preparation Example 7 was repeated, except that 2.95 g of 4-aminobenzonitrile was used in place of 4-aminophenol. The resulting crude product was purified by silica gel column chromatography (using a 4:1 mixture of hexane and ethyl acetate as the eluent) to  
15 obtain 5.194 g of 4-[N-(4-benzyloxybenzyl)amino]-benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.40(2H, d,  $J=3.0\text{Hz}$ ), 4.4(1H, br), 5.06(2H, s), 6.56(2H, d,  $J=5.8\text{Hz}$ ), 6.78-7.52(11H, m).

MS(m/z): 314( $\text{M}^+$ ).

20

#### Preparation Example 41

The procedure of Preparation Example 38 was repeated, except that 314 mg of 4-[N-(4-benzyloxybenzyl)amino]benzonitrile was used in place of 4-[N-(3-pyridyl)amino]benzonitrile, and 142 mg of  
25 methyl iodide was used in place of 4-benzyloxybenzyl chloride. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 173 mg of 4-[N-(4-benzyloxybenzyl)-N-methylamino]benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.08(3H, s), 4.56(2H, d,  $J=5.8\text{Hz}$ ), 5.05(2H, s),  
30 6.42-7.55(13H, m).

MS(m/z): 328( $\text{M}^+$ ).

Preparation Example 42

The procedure of Preparation Example 9 was repeated, except that 164 mg of 4-[N-(4-benzyloxybenzyl)-N-methylamino]benzonitrile was used in place of 4-[N-(4-benzyloxybenzyl)-N-methylsulfonylamino]-phenyl methanesulfonate, and 3 ml of ethyl acetate was used in place of dioxane. The resulting mixture was stirred for 4 hours under an atmospheric pressure of hydrogen. The reaction mixture was filtered to remove any insoluble matter, and the solvent was distilled off from the filtrate. The resulting crude product was purified by TLC (using a 1:1 mixture of ethyl acetate and hexane as the developing solvent) to obtain 44 mg of 4-[N-(4-hydroxybenzyl)-N-methylamino]benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.09(3H, s), 4.52(2H, s), 6.43-7.57(8H, m).

MS(m/z): 238( $\text{M}^+$ ).

15 Preparation Example 43

The procedure of Preparation Example 38 was repeated, except that 314 mg of 4-[N-(4-benzyloxybenzyl)amino]benzonitrile was used in place of 4-[N-(3-pyridyl)amino]benzonitrile, and 156 mg of ethyl iodide was used in place of 4-benzyloxybenzyl chloride. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 114 mg of 4-[N-(4-benzyloxybenzyl)-N-ethylamino]benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.22(3H, t,  $J=4.7\text{Hz}$ ), 3.50(2H, q,  $J=4.7\text{Hz}$ ), 4.55(2H, d,  $J=5.8\text{Hz}$ ), 5.05(2H, s), 6.64(2H, d,  $J=6.0\text{Hz}$ ), 6.93(2H, d,  $J=5.3\text{Hz}$ ), 7.07(2H, d,  $J=6.0\text{Hz}$ ), 7.17-7.56(7H, m).

MS(m/z): 342( $\text{M}^+$ ).

Preparation Example 44

The procedure of Preparation Example 9 was repeated, except that 111 mg of 4-[N-(4-benzyloxybenzyl)-N-ethylamino]benzonitrile was used in place of 4-[N-(4-benzyloxybenzyl)-N-methylsulfonylamino]phenyl

methanesulfonate, and 3 ml of ethyl acetate was used in place of dioxane. The resulting mixture was stirred for 4 hours under an atmospheric pressure of hydrogen. The reaction mixture was filtered to remove any insoluble matter, and the solvent was distilled off from the filtrate. The resulting crude product was purified by TLC (using a 1:1 mixture of ethyl acetate and hexane as the developing solvent) to obtain 29 mg of 4-[N-ethyl-N-(4-hydroxybenzyl)amino]benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 1.22(3H, t,  $J=4.7\text{Hz}$ ), 3.50(2H, q,  $J=4.7\text{Hz}$ ), 4.49(2H, s), 6.45-7.55(8H, m).

10 MS(m/z): 252( $\text{M}^+$ ).

#### Preparation Example 45

The procedure of Preparation Example 7 was repeated, except that 2.058 g of 4-(tert-butyldimethylsilyloxy)benzyl chloride was used in place of 4-benzyloxybenzyl chloride, and 0.946 g of 4-aminobenzonitrile was used in place of 4-aminophenol. The resulting crude product was purified by silica gel column chromatography (using a 3:1 mixture of hexane and ethyl acetate as the eluent) to obtain 0.682 g of 4-[N-(4-tert-butyldimethylsilyloxybenzyl)amino]benzonitrile.

20  $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 0.17(6H, s), 0.96(9H, s), 4.23(2H, d,  $J=5.2\text{Hz}$ ), 4.6(1H, br), 6.63(2H, d,  $J=8.4\text{Hz}$ ), 6.79(2H, d,  $J=8.2\text{Hz}$ ), 7.17(2H, d,  $J=8.2\text{Hz}$ ), 7.33(2H, d,  $J=8.4\text{Hz}$ ).

#### Preparation Example 46

25 The procedure of Preparation Example 8 was repeated, except that 195 mg of 4-[N-(4-tert-butyldimethylsilyloxybenzyl)amino]benzonitrile was used in place of 4-[N-(4-benzyloxybenzyl)amino]phenol, and 84 mg of 2-thiophenecarbonyl chloride was used in place of methanesulfonyl chloride. The resulting mixture was stirred at room temperature for 19 hours. After the reaction mixture was poured into dilute hydrochloric acid, the product was extracted with ethyl acetate. After the extract



was successively washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was purified by  
 5 TLC (using a 3:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 196 mg of N-(4-tert-butyldimethylsilyloxybenzyl)-N-(4-cyanophenyl)-2-thiophenecarboxamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 0.17(6H, s), 0.96(9H, s), 5.00(2H, s),  
 6.60-7.67(11H, m).

10 MS(m/z): 448( $\text{M}^+$ ).

#### Preparation Example 47

180 mg of N-(4-tert-butyldimethylsilyloxybenzyl)-N-(4-cyanophenyl)-2-thiophenecarboxamide was dissolved in 3.5 ml of tetrahydro-  
 15 furan, and 386 mg of tetrabutylammonium fluoride was added thereto under cooling with ice, followed by stirring at room temperature for 4 hours. After the reaction mixture was poured into a saturated aqueous solution of sodium chloride, the product was extracted with diethyl ether. After the extract was dried over anhydrous magnesium sulfate,  
 20 the solvent was distilled off under reduced pressure. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 47 mg of N-(4-cyanophenyl)-N-(4-hydroxybenzyl)-2-thiophenecarboxamide.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 5.02(2H, s), 6.56-7.76(11H, m).

25 MS(m/z): 334( $\text{M}^+$ ).

#### Preparation Example 48

The procedure of Preparation Example 8 was repeated, except that 203 mg of 4-[N-(4-tert-butyldimethylsilyloxybenzyl)amino]benzo-  
 30 nitrile was used in place of 4-[N-(4-benzyloxybenzyl)amino]phenol, and 110 mg of 3-thiophenecarbonyl chloride was used in place of methane-

sulfonyl chloride. The resulting mixture was stirred at room temperature for 19 hours. After the reaction mixture was poured into dilute hydrochloric acid, the product was extracted with ethyl acetate. After the extract was successively washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate, the solvent was distilled off under reduced pressure. The resulting crude product was purified by TLC (using a 3:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 191 mg of N-(4-tert-butyl-  
 5 dimethylsilyloxybenzyl)-N-(4-cyanophenyl)-3-thiophenecarboxamide.  
 10

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 0.17(6H, s), 0.96(9H, s), 5.03(2H, s),  
 6.61-7.60(11H, m).

MS(m/z): 448( $\text{M}^+$ ).

15 Preparation Example 49

The procedure of Preparation Example 47 was repeated, except that 180 mg of N-(4-tert-butyl dimethylsilyloxybenzyl)-N-(4-cyanophenyl)-3-thiophenecarboxamide was used in place of N-(4-tert-butyl dimethylsilyloxybenzyl)-N-(4-cyanophenyl)-2-thiophenecarbox-  
 20 amide. Thus, there was obtained 60 mg of N-(4-cyanophenyl)-N-(4-hydroxy-benzyl)-3-thiophenecarboxamide.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 5.04(2H, s), 6.55-7.70(11H, m).

MS(m/z): 334( $\text{M}^+$ ).

25 Preparation Example 50

The procedure of Preparation Example 38 was repeated, except that 504 mg of N-(4-cyanophenyl)-4-methoxybenzamide was used in place of 4-[N-(3-pyridyl)amino]benzonitrile, and 707 mg of methyl iodide was used in place of 4-benzyloxybenzyl chloride. Thus, there was  
 30 obtained 620 mg of a crude product of N-(4-cyanophenyl)-4-methoxy-N-methylbenzamide.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 3.45(3H, s), 3.72(3H, s), 6.70(2H, d,  $J=8.4\text{Hz}$ ), 7.15(2H, d,  $J=8.4\text{Hz}$ ), 7.23(2H, d,  $J=8.4\text{Hz}$ ), 7.55(2H, d,  $J=8.4\text{Hz}$ ).

#### Preparation Example 51

5           The procedure of Preparation Example 2 was repeated, except that 556 mg of N-(4-cyanophenyl)-4-methoxy-N-methylbenzamide was used in place of 4'-methoxy-2-biphenylacetonitrile. Thus, there was obtained 463 mg of a crude product of N-(4-cyanophenyl)-4-hydroxy-N-methylbenzamide.

10            $^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$ : 3.27(3H, s), 6.42-7.40 (8H, m).  
MS(m/z): 252( $\text{M}^+$ ).

#### Preparation Example 52

451 mg of 3-methoxy-N-(2-methoxyphenyl)benzamide and 1.58  
15 g of pyridine hydrochloride were mixed, and stirred on an oil bath at 190°C for 2 hours. After cooling, dilute hydrochloric acid was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium  
20 solvent was distilled off, the resulting crude product was recrystallized from methanol to obtain 109 mg of 3-hydroxy-N-(2-hydroxyphenyl)benzamide.

$^1\text{H-NMR}(\text{DMSO-d}_6, \delta)$ : 6.9-7.1(1H, m), 7.2-7.9(9H, m), 9.90(1H, s).  
MS(m/z): 211( $\text{M}^+ - \text{H}_2\text{O}$ ).

25

#### Preparation Example 53

The procedure of Preparation Example 52 was repeated, except that 536 mg of 3-methoxy-N-(4-methoxyphenyl)benzamide was used in place of 3-methoxy-N-(2-methoxyphenyl)benzamide. The  
30 resulting crude product was crystallized from diethyl ether to obtain 127 mg of 3-hydroxy-N-(4-hydroxyphenyl)benzamide.

$^1\text{H-NMR}$ (DMSO- $d_6$ ,  $\delta$ ): 6.73(2H, d,  $J=7\text{Hz}$ ), 6.8-7.4(4H, m), 7.50(2H, d,  $J=8.8\text{Hz}$ ), 9.4(2H, br), 9.87(1H, br s).

MS( $m/z$ ): 229( $M^+$ ), 121.

#### 5 Preparation Example 54

The procedure of Preparation Example 25 was repeated, except that 392 mg of 4-[N-(2-pyrazinyl)amino]benzonitrile was used in place of 4-[N-(4-methoxyphenyl)amino]benzonitrile. Thus, there was obtained 445 mg of 4-[N-(4-hydroxybenzyl)-N-(2-pyrazinyl)amino]benzo-

10 nitrile.

$^1\text{H-NMR}$ ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 5.19(2H, s), 6.68(2H, d,  $J=5.5\text{Hz}$ ), 7.06(2H, d,  $J=5.5\text{Hz}$ ), 7.40(2H, d,  $J=5.8\text{Hz}$ ), 7.67(2H, d,  $J=5.8\text{Hz}$ ) 7.80-8.27 (3H, m).

MS( $m/z$ ): 302( $M^+$ ).

15

#### Preparation Example 55

The procedure of Example 40 was repeated, except that 1.43 g of 4-aminobenzonitrile was used in place of aniline, and 1.57 g of 2-thiophenecarbaldehyde was used in place of 4-formyl-phenyl sulfamate.

20 The resulting crude product was purified by silica gel column chromatography (using a 2:1 mixture of hexane and ethyl acetate as the eluent) to obtain 0.98 g of 4-[N-(2-thenyl)amino]-benzonitrile.

$^1\text{H-NMR}$ ( $\text{CDCl}_3$ ,  $\delta$ ): 4.56(2H, s), 6.46-6.76(2H, m), 6.87-7.83(5H, m).

MS( $m/z$ ): 214( $M^+$ ).

25

#### Preparation Example 56

The procedure of Preparation Example 25 was repeated, except that 428 mg of 4-[N-(2-thenyl)amino]benzonitrile was used in place of 4-[N-(4-methoxyphenyl)amino]benzonitrile. Thus, there was

30 obtained 349 mg of 4-[N-(4-hydroxybenzyl)-N-(2-thenyl)amino]benzo-nitrile.

$^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 4.60(2H, s), 4.83(2H, s), 6.55-7.55(11H, m).  
 MS(m/z): 320( $\text{M}^+$ ).

#### Preparation Example 57

5           The procedure of Example 40 was repeated, except that 1.43 g of 4-aminobenzonitrile was used in place of aniline, and 1.57 g of 3-thiophenecarbaldehyde was used in place of 4-formyl-phenyl sulfamate. The resulting crude product was purified by silica gel column chromatography (using a 2:1 mixture of hexane and ethyl acetate as the  
 10 eluent) to obtain 1.00 g of 4-[N-(3-thenyl)amino]-benzonitrile.

$^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 4.40(2H, s), 6.44-6.73(2H, m), 6.90-7.56(5H, m).  
 MS(m/z): 214( $\text{M}^+$ ).

#### Preparation Example 58

15           The procedure of Preparation Example 25 was repeated, except that 428 mg of 4-[N-(3-thenyl)amino]benzonitrile was used in place of 4-[N-(4-methoxyphenyl)amino]benzonitrile. Thus, there was obtained 391 mg of 4-[N-(4-hydroxybenzyl)-N-(3-thenyl)amino]benzo-  
 nitrile.

20            $^1\text{H-NMR}(\text{CD}_3\text{OD}, \delta)$ : 4.62(2H, s), 4.67(2H, s), 6.60-7.53(11H, m).  
 MS(m/z): 320( $\text{M}^+$ ).

#### Preparation Example 59

A mixture composed of 500 mg of N-(4-bromophenyl)methane-  
 25 sulfonamide, 334 mg of 4-methoxyphenyl boronic acid, 55.5 mg of tetrakis-triphenylphosphinepalladium, 2 ml of a 2 M aqueous solution of sodium carbonate, 4 ml of toluene, and 1 ml of ethanol was heated under reflux for 5 hours in an atmosphere of nitrogen. After the reaction mixture was poured into a saturated aqueous solution of sodium  
 30 chloride, the product was extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium

sulfate. After the solvent was distilled off, the resulting crude product was purified by silica gel column chromatography (using a 7:1 mixture of chloroform and tetrahydrofuran as the eluent) to obtain 94 mg of N-(4'-methoxybiphenyl-4-yl)methanesulfonamide.

- 5         $^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 2.98(3H, s), 3.79(3H, s), 7.00(2H, d,  $J=8.7\text{Hz}$ ), 7.26(2H, d,  $J=8.7\text{Hz}$ ), 7.55(2H, d,  $J=8.7\text{Hz}$ ), 7.57(2H, d,  $J=8.7\text{Hz}$ ), 9.72(1H, s).  
MS( $m/z$ ): 277( $M^+$ ), 198.

#### 10    Preparation Example 60

- The procedure of Preparation Example 2 was repeated, except that 55 mg of N-(4'-methoxybiphenyl-4-yl)methanesulfonamide was used in place of 4'-methoxy-2-biphenylacetonitrile, and 1,2-dichloroethane was used in place of methylene chloride. The resulting crude product was  
15    purified by TLC (using a 6:1 mixture of chloroform and acetone as the developing solvent) to obtain 24 mg of N-(4'-hydroxybiphenyl-4-yl)-methanesulfonamide.

- $^1\text{H-NMR}(\text{DMSO-}d_6, \delta)$ : 2.98(3H, s), 6.82(2H, d,  $J=8.7\text{Hz}$ ), 7.24(2H, d,  $J=8.7\text{Hz}$ ), 7.43(2H, d,  $J=8.7\text{Hz}$ ), 7.53(2H, d,  $J=8.7\text{Hz}$ ), 9.45(1H, s),  
20    9.69(1H, s).  
MS( $m/z$ ): 263( $M^+$ ), 184.

#### Preparation Example 61

- The procedure of Preparation Example 59 was repeated,  
25    except that 500 mg of N-(2-bromophenyl)methanesulfonamide was used in place of N-(4-bromophenyl)methanesulfonamide. The resulting crude product was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as the developing solvent) to obtain 441 mg of N-(4'-methoxybiphenyl-2-yl)methanesulfonamide.

- 30         $^1\text{H-NMR}(\text{CDCl}_3, \delta)$ : 2.88(3H, s), 3.87(3H, s), 6.50(1H, s), 7.02(2H, d,  $J=8.9\text{Hz}$ ), 7.1-7.4(5H, m), 7.64(1H, d,  $J=8.0\text{Hz}$ ).

MS(m/z): 277(M<sup>+</sup>), 198.

### Preparation Example 62

The procedure of Preparation Example 2 was repeated, except  
 5 that 208 mg of N-(4'-methoxybiphenyl-2-yl)methanesulfonamide was used  
 in place of 4'-methoxy-2-biphenylacetonitrile, and 1,2-dichloro-ethane  
 was used in place of methylene chloride. The resulting crude product  
 was purified by TLC (using a 2:1 mixture of hexane and ethyl acetate as  
 the developing solvent) to obtain 178 mg of N-(4'-hydroxy-biphenyl-2-  
 10 yl)methanesulfonamide.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 2.67(3H, s), 6.82(2H, d, J=8.5Hz), 7.2-7.4  
 (6H, m), 8.74(1H, s), 9.48(1H, s).

MS(m/z): 263(M<sup>+</sup>), 184.

### 15 Preparation Example 63

The procedure of Preparation Example 8 was repeated, except  
 that 601 mg of 4'-methoxybiphenyl-4-ol was used in place of 4-[N-(4-  
 benzyloxybenzyl)amino]phenol. The resulting mixture was stirred at  
 room temperature for 19 hours. After the reaction mixture was poured  
 20 into dilute hydrochloric acid, the precipitated crystals were separated by  
 filtration to obtain 783 mg of a crude product of 4'-methoxybiphenyl-4-yl  
 methanesulfonate.

The procedure of Preparation Example 2 was repeated, except  
 that 500 mg of the crude product of 4'-methoxybiphenyl-4-yl methane-  
 25 sulfonate was used in place of 4'-methoxy-2-biphenylacetonitrile. The  
 resulting crude product was purified by TLC (using a 8:1 mixture of  
 chloroform and tetrahydrofuran as the developing solvent) to obtain 250  
 mg of 4'-hydroxybiphenyl-4-yl methanesulfonate.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 3.37(3H, s), 6.85(2H, d, J=8.6Hz), 7.37(2H, d,  
 30 J=8.6Hz), 7.49(2H, d, J=8.6Hz), 7.66(2H, d, J=8.6Hz), 9.56(1H, s).

MS(m/z): 264(M<sup>+</sup>), 185.

#### Preparation Example 64

The procedure of Preparation Example 2 was repeated, except that 224 mg of (2Z)-2,3-bis(4-methoxyphenyl)prop-2-enenitrile was used in place of 4'-methoxy-2-biphenylacetonitrile, and 1,2-dichloroethane was  
5 used in place of methylene chloride. The resulting crude product was purified by TLC (using a 3:1 mixture of chloroform and acetone as the developing solvent) to obtain 130 mg of (2Z)-2,3-bis(4-hydroxyphenyl)-prop-2-enenitrile.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD, δ): 6.87(4H, d, J=8.8Hz), 7.3-7.6(3H, m), 7.78(2H, d, J=8.8Hz).  
10

MS(m/z): 237(M<sup>+</sup>).

#### Preparation Example 65

The procedure of Preparation Example 28 was repeated,  
15 except that 1.145 g of 2-chloropyrimidine was used in place of 4-fluorobenzonitrile. The precipitated crystals were separated by filtration to obtain 691 mg of a crude product of 4-[N-(2-pyrimidyl)amino]benzonitrile.

The procedure of Preparation Example 38 was repeated,  
20 except that 298 mg of the crude product of 4-[N-(2-pyrimidyl)amino]benzonitrile was used in place of 4-[N-(3-pyridyl)amino]benzonitrile, and 390 mg of 4-(tert-butyldimethylsilyloxy)benzyl chloride was used in place of 4-benzyloxybenzyl chloride. The resulting crude product was purified by TLC (using a 1:1 mixture of ethyl acetate and hexane as the  
25 developing solvent) to obtain 228 mg of 4-[N-(4-tert-butyldimethylsilyloxybenzyl)-N-(2-pyrimidyl)amino]benzonitrile.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>, δ): 0.20(6H, s), 0.99(9H, s), 4.94(2H, s), 6.86(2H, d, J=8.0Hz), 7.04(2H, d, J=8.0Hz), 7.32(2H, d, J=8.5Hz), 7.5-8.0(4H, m), 8.3-8.6(1H, m).  
30 MS(m/z): 416(M<sup>+</sup>), 221, 195.



Preparation Example 66

The procedure of Preparation Example 47 was repeated, except that 211 mg of 4-[N-(4-tert-butyldimethylsilyloxybenzyl)-N-(2-pyrimidyl)amino]benzonitrile was used in place of N-(4-tert-butyl-  
 5 dimethylsilyloxybenzyl)-N-(4-cyanophenyl)-2-thiophenecarboxamide. The resulting crude product was purified by TLC (using a 19:1 mixture of chloroform and methanol as the developing solvent) to obtain 89 mg of 4-[N-(4-hydroxybenzyl)-N-(2-pyrimidyl)amino]benzonitrile.

<sup>1</sup>H-NMR(CD<sub>3</sub>OD, δ): 5.03(2H, d, J=4.5Hz), 6.78(2H, d, J=8.3Hz),  
 10 7.06(2H, d, J=8.3Hz), 7.50(2H, d, J=8.0Hz), 7.6-8.7(5H, m).  
 MS(m/z): 302(M<sup>+</sup>), 195, 107.

Preparation Example 67

The procedure of Example 96 was repeated, except that 661 mg  
 15 of 4-aminobenzyl cyanide was used in place of 4'-aminobiphenyl-4-ol, and 7.5 ml of N,N-dimethylacetamide and 635 mg of sulfamoyl chloride were used. Thus, there was obtained 951 mg of a crude product of amino[4-(cyanomethyl)phenyl]sulfonamide.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 3.92(2H, s), 7.08(2H, s), 7.16(2H, d, J=8.8Hz),  
 20 7.24(2H, d, J=8.8Hz), 9.52(1H, s).  
 MS(m/z): 211(M<sup>+</sup>), 131.

Preparation Example 68

A mixture composed of 738 mg of the crude product of  
 25 amino[4-(cyanomethyl)phenyl]sulfonamide, 0.425 ml of 4-anisaldehyde, 524 mg of potassium carbonate, and 3.5 ml of methanol was heated under reflux for 2 hours. After the reaction mixture was poured into water and acidified with dilute hydrochloric acid, the product was extracted with ethyl acetate. The organic layer was washed with water  
 30 and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the resulting crude product was purified by silica gel column

chromatography (using a 2:1 mixture of chloroform and tetrahydrofuran as the eluent) to obtain 98 mg of (2Z)-2-[4-(sulfamoylamino)-phenyl]-3-(4-methoxyphenyl)prop-2-enenitrile.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 3.84(3H, s), 7.10(2H, d, J=8.6Hz), 7.21(2H, s),  
5 7.25(2H, d, J=8.6Hz), 7.63(2H, d, J=8.6Hz), 7.82(1H, s), 7.91(2H, d,  
J=8.6Hz), 9.78(1H, s).

MS(m/z): 329(M<sup>+</sup>), 250.

#### Preparation Example 69

10 The procedure of Preparation Example 2 was repeated, except  
that 63 mg of (2Z)-2-[4-(N-sulfamoylamino)phenyl]-3-(4-methoxyphenyl)-  
prop-2-enenitrile was used in place of 4'-methoxy-2-biphenylacetonitrile,  
and 1,2-dichloroethane was used in place of methylene chloride. The  
resulting crude product was purified by TLC (using a 2:1 mixture of  
15 chloroform and acetone as the developing solvent) to obtain 17 mg of  
(2Z)-2-[4-(sulfamoylamino)phenyl]-3-(4-hydroxyphenyl)prop-2-enenitrile.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 6.89(2H, d, J=8.8Hz), 7.19(2H, s), 7.24(2H, d,  
J=8.8Hz), 7.60(2H, d, J=9.0Hz), 7.74(1H, s), 7.81(2H, d, J=9.0Hz),  
9.74(1H, s), 10.14(1H, s).

20 MS(m/z): 315(M<sup>+</sup>), 236.

#### Preparation Example 70

The procedure of Preparation Example 2 was repeated, except  
that 1.465 g of methyl 4-[(1Z)-2-cyano-2-(4-methoxyphenyl)vinyl]phenyl-  
25 carboxylate was used in place of 4'-methoxy-2-biphenylacetonitrile, and  
1,2-dichloroethane was used in place of methylene chloride. The  
resulting crude product was purified by TLC (using a 10:1 mixture of  
chloroform and tetrahydrofuran as the developing solvent) to obtain 524  
mg of methyl 4-[(1Z)-2-cyano-2-(4-hydroxyphenyl)vinyl]phenylcarboxy-  
30 late.

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>, δ): 3.89(3H, s), 6.90(2H, d, J=8.7Hz), 7.63(2H, d,

$J=8.7\text{Hz}$ ), 7.92(1H, s), 8.00(2H, d,  $J=8.4\text{Hz}$ ), 8.06(2H, d,  $J=8.4\text{Hz}$ ), 10.00(1H, s).

MS( $m/z$ ): 279( $M^+$ ), 248, 220.

10019693 010303

## Tablets:

	<u>mg/tablet</u>
Active ingredient	5.0
Starch	10.0
5 Lactose	73.0
Carboxymethyl cellulose calcium salt	10.0
Talc	1.0
<u>Magnesium stearate</u>	<u>1.0</u>
	100.0

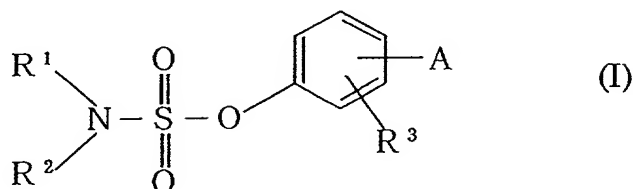
10

The active ingredient is pulverized to a particle size of 70 microns or less. Then, starch, lactose and carboxymethyl cellulose calcium salt are added thereto and thoroughly mixed therewith. After the addition of 10% starch paste, the above powder mixture is agitated and blended to prepare granules. After drying, these granules are adjusted to a particle diameter of about 1,000 microns, and mixed with talc and magnesium stearate. The resulting mixture is formed into tablets.

15

## CLAIMS

1. A phenyl sulfamate derivative represented by the following formula, or a salt thereof.



wherein

$R^1$  and  $R^2$  each independently represent a hydrogen atom or a lower alkyl group;

$R^3$  represents a hydrogen atom, a halogen atom, a lower alkyl group,  $-\text{OSO}_2\text{NR}^1\text{R}^2$ , a lower alkanoylamino group, a nitro group or a cyano group; and

A represents a substituted or unsubstituted phenyl group, a naphthyl group, a pyridyl group, 2-substituted thiazol-4-yl group, 3-substituted isoxazol-5-yl group, 1-cyano-2-(substituted or unsubstituted phenyl)vinyl group, 2-cyano-2-(substituted or unsubstituted phenyl)vinyl group, or a group of the formula  $-\text{X}-\text{NR}^4\text{R}^5$  [in which X represents CO or  $\text{CH}_2$ ,  $R^4$  represents a hydrogen atom, a lower alkyl group, a substituted or unsubstituted phenyl group, a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, a sulfamoyl group, a lower alkanoylamino group, a di(lower alkyl)amino group, a heteroaryl group, a heteroaryl-substituted lower alkyl group, or a substituted or unsubstituted phenylmethyl group, and  $R^5$  represents a hydrogen atom, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted phenylcarbonyl group, provided that

① when X represents CO,  $R^4$  represents a group other than a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl

group, and  $R^5$  represents a group other than a substituted or unsubstituted phenylcarbonyl group;

② when  $R^4$  represents a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, or a sulfamoyl group, X represents  $CH_2$  and  $R^5$  represents a group other than a substituted or unsubstituted phenylcarbonyl group; and

③ when  $R^5$  represents a substituted or unsubstituted phenylcarbonyl group, X represents  $CH_2$  and  $R^4$  represents a group other than a lower alkanoyl group, a substituted or unsubstituted phenylcarbonyl group, a heteroarylcarbonyl group, a lower alkylsulfonyl group, and a sulfamoyl group]; or

$R^3$  and A, together with the phenyl group to which they are attached, represent a fluoren-2-yl or 9-oxofluoren-2-yl group;

provided that, when  $R^3$  represents a hydrogen atom, A does not represent an unsubstituted phenyl group.

2. A phenyl sulfamate derivative or a salt thereof as claimed in claim 1 wherein both  $R^1$  and  $R^2$  represent hydrogen atoms.

3. A phenyl sulfamate derivative or a salt thereof as claimed in claim 1 or 2 wherein  $R^3$  represents a hydrogen atom or a halogen atom.

4. A phenyl sulfamate derivative or a salt thereof as claimed in any of claims 1 to 3 wherein A is located at the 4-position.

5. A phenyl sulfamate derivative or a salt thereof as claimed in any of claims 1 to 4 wherein A represents a substituted phenyl group or a group of the formula  $-X-NR^4R^5$ .

6. A phenyl sulfamate derivative or a salt thereof as claimed in

claim 5 wherein the substituted phenyl group is a phenyl group substituted by one or two substituents selected from halogen, lower alkyl, halogen-substituted lower alkyl, cyano-substituted lower alkyl, lower alkoxy, lower alkanoyloxy,  $-\text{OSO}_2\text{NR}^1\text{R}^2$ , organic sulfonyloxy, amino, lower alkanoylamino,  $-\text{NHSO}_2\text{NR}^1\text{R}^2$ , organic sulfonylamino, nitro, cyano, carboxyl and lower alkoxycarbonyl.

7. A phenyl sulfamate derivative or a salt thereof as claimed in claim 6 wherein, in the substituted phenyl group, the substituent or substituents are located at the 2- and/or 4-positions of the phenyl group.

8. A phenyl sulfamate derivative or a salt thereof as claimed in claim 5 wherein A represents a group of the formula  $-\text{X}-\text{NR}^4\text{R}^5$  and  $\text{R}^4$  represents a hydrogen atom, a lower alkyl group or a heteroaryl group.

9. A phenyl sulfamate derivative or a salt thereof as claimed in claim 8 wherein the heteroaryl group is a five- or six-membered monocyclic heteroaryl group containing 1 to 3 nitrogen atoms.

10. A phenyl sulfamate derivative or a salt thereof as claimed in claim 5 wherein  $\text{R}^5$  represents a substituted phenyl group.

11. A phenyl sulfamate derivative or a salt thereof as claimed in claim 10 wherein the substituted phenyl group is a phenyl group substituted by one or two substituents selected from hydroxyl, lower alkanoyloxy,  $-\text{OSO}_2\text{NR}^1\text{R}^2$ , nitro and cyano.

12. A steroid sulfatase inhibitor containing, as an active ingredient, a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in any of claims 1 to 11.

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13. An agent for the treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease, which contains, as an active ingredient, a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in any of claims 1 to 11.
14. A pharmaceutical composition comprising a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in any of claims 1 to 11, and a pharmaceutically acceptable adjuvant.
15. The use of a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in any of claims 1 to 11, for the prophylaxis or treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease.
16. A method for the prophylaxis or treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease in a human being or other mammal which comprises administering a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in any of claims 1 to 11, to the human being or other mammal.
17. The use of a phenyl sulfamate derivative of formula (I) or a salt thereof as claimed in any of claims 1 to 11, for the preparation of an agent for the treatment of breast cancer, corpus uteri cancer, endometrial hyperplasia, infertility, endometriosis, adenomyosis uteri, autoimmune diseases, dementia or Alzheimer's disease.



# DECLARATION AND POWER OF ATTORNEY FOR U. S. PATENT APPLICATION

☒ Original ☐ Supplemental ☐ Substitute ☐ PCT ☐ Design

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: PHENYL SULFAMATE DERIVATIVES

of which is described and claimed in:

- ☐ the attached specification, or  
☐ the specification in the application Serial No. \_\_\_\_\_ filed \_\_\_\_\_;  
 and with amendments through \_\_\_\_\_ (if applicable), or  
☒ the specification in International Application No. PCT/JP00/04427, filed Jul. 4, 2000, and as amended  
 on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:


COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Japan	191,632/99	July 6, 1999	Yes

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

And I hereby appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; and Michael S. Huppert, Reg. No. 40,268, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys and agents named herein to accept and follow instructions from ODAJIMA & CO. as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

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I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1st Inventor Naoyuki Koizumi Date December 25, 2001

2nd Inventor Makoto Okada Date December 25, 2001

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5th Inventor Takayoshi Nakagawa Date December 25, 2001

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7th Inventor Tomohito Fujii Date December 25, 2001

The above application may be more particularly identified as follows:

U.S. Application Serial No. \_\_\_\_\_ Filing Date \_\_\_\_\_

Applicant Reference Number \_\_\_\_\_ Atty Docket No. \_\_\_\_\_

Title of Invention \_\_\_\_\_